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IMPORTANT CONTRIBUTIONS TO CLINICAL MEDICINE DURING THE PAST THIRTY YEARS FROM THE STUDY OF HUMAN BLOOD PRESSURE.[1]

By Theodore C. Janeway, M. D., Baltimore.

INTRODUCTION.

Although Vierordt's crude attempts to measure the compressibility of the pulse by the attachment of weights to a sphygmograph were made many years before, the clinical study of blood pressure really dates from the publication by von Basch, in 1881, of work done with his first sphygmomanometer. When this association first met, 30 years ago, interest in the new method was confined to von Basch and his immediate pupils, and neither the transactions of this society nor the standard text-books on practice of the day make the slightest reference to the method or its results. In the sixth edition of Flint's "Practice of Medicine," published in 1886, in the preparation of which Dr. William H. Welch assisted, and which represented the best clinical knowledge of that time, one finds statements such as these:

"A well-recognized form of cardiac hypertrophy is that which is secondary to certain forms of chronic Bright's disease, particularly to the small granular kidneys. The explanation of this is not thoroughly understood. It will be referred to under the head of Bright's Disease. Suffice it to say here that it is probably due to some resistance to the blood current through the small vessels"; and "As already stated, simple hypertrophy of the left ventricle of the heart may have a causative relation to cerebral hemorrhage by increasing arterial tension." In describing the clinical history of apoplexy he says: "The pulse is usually diminished in frequency, full and hard, the artery striking against the finger like a metal rod."

These quotations show the clear recognition, by the unaided senses of the clinician, of the existence and associations of high blood pressure, but no material advance in its detection or in the study of the problems presented by it since the days of Richard Bright half a century before.

In 1891 an important paper on Bright's disease was presented before this association by Dr. Francis Delafield.[2] In it he speaks frequently of contraction of the arteries and of the disturbance of the circulation, to which he attributes the cerebral symptoms and dropsy of nephritis and for which he advocates drugs which dilate the arteries. The same year a discussion of the relations between arterial disease and visceral

[1] Read at the thirtieth annual meeting of the Association of American Physicians, Washington, May 11, 1915.

[2] Delafield, Francis: On the diseases of the kidneys popularly called Bright's disease. Tran. Assn. Amer. Phys., 1891, VI, 124-154.

changes was led by Drs. Peabody [3] and Councilman,[4] and participated in by such distinguished clinicians as Drs. Ord and Gairdner, with casual allusions to increased arterial tension and spasm of the arteries, but no reference whatsoever to the existence of any clinical knowledge of blood pressure.

In 1899, Dr. Stengel read a paper upon the immediate and remote effects of athletics upon the heart and circulation, without making any mention of blood pressure, and in the discussion which followed Dr. Meigs made this remarkable statement:

> The doctrines that were generally accepted 20 years ago in regard to Bright's disease and the hypertrophy of the heart so commonly associated with it have fallen almost entirely into discredit. We used to be told that kidney disease caused increased resistance within the arteries, and this threw more work upon the heart, which in answer underwent hypertrophy and grew strong. Little is heard of this any more, and Bright's disease is less and less frequently used as a diagnostic term.

The first paper that dealt with blood pressure specifically was the important presentation at the twelfth meeting, in 1897, by Abel and Crawford, of the isolation of chemically pure epinephrin.[5] This was, however, experimental work.

The first report of observations on human blood pressure was made in 1903 by Dr. Richard C. Cabot, as part of a paper describing "Studies on the Action of Alcohol in Disease, Especially upon the Circulation." This was a careful clinical study of a therapeutic problem in 58 cases, the Riva-Rocci sphygmomanometer and the original Oliver hemodynamometer being the instruments employed.

At the meeting in 1904 another paper by Dr. Cabot [6] dealt altogether with blood pressure measurements, and two by Dr. Stengel [7] contained studies on arterial pressure. One of these [8] was in collaboration with the late Dr. W. B. Stanton, who played an important part in securing the adoption of the sphygmomanometer by the American practitioner as part of his armamentarium.

From the year 1906, when the association so kindly endured my maiden presentation on hypertension, to the present time, no meeting has been without several papers on blood pressure problems, clinical or experimental, and for the past seven years all have shown that clinical blood pressure measurements have become a permanent part of the routine examination of the circulatory system.

In 1886 the literature of human arterial pressure, so far as I have been able to collect it, comprised twelve titles. It is not wholly without regret that I find that my personal bibliographic references in this field for the past ten years amount to more than one thousand titles. From this mass of accumulated knowledge of the behavior of the blood pressure in health and disease, what real gain has there been to clinical medicine?

I. A Method of Observation.

A method of sufficient accuracy and sufficient ease of application to satisfy the requirements of medical practice is now available. The contributions toward the elaboration of our present instruments and the methods of their application for the determination of the systolic and the diastolic pressures, and the critical studies to which they have been subjected, are among the most important that I have to record.

To von Basch we owe the first real sphygmomanometer and the first observations of human blood pressure which have any value. Potain [9] in 1899 made the first important modification by introducing air in place of water as the medium for the transmission of the pressure. In 1896 Riva-Rocci,[10] and in 1897 Leonard Hill,[11] independently devised the method of circular compression by which the main inaccuracies in the application of the sphygmomanometer were overcome. In 1901 von Recklinghausen [12] demonstrated that the chief error which remained was dependent upon too narrow a compressing armlet, and introduced the wide cuff which has since become universal. In 1905 Korotkow [13] published his method of auscultatory determination, which has supplanted all other methods for the clinical measurement of the diastolic arterial pressure.

At the present day accurate sphygmomanometers of varying types, to suit the requirements of hospital, consulting room and family practice, are obtainable in every country. An accurate sphygmomanometer consists of a tested manometer, a compressing bag 12 cm. in width for the arm, an inflator fitted with a needle-valve for the slow release of pressure, and connecting tubing. Many types of instrument now discarded have contributed to the production of the present form and have been of great service in the critical study of methods—especially the early instruments of Marey and Mosso, by which diastolic pressures were first approximately studied, the graphic instrument of Erlanger, the various portable instruments of George Oliver, and the instruments of Hill and Barnard and of Gibson. In this country H. W. Cook first introduced a portable form of the Riva-Rocci apparatus. The tonometer of Gärtner was undoubtedly a factor in promoting clinical studies of blood pressure, though its usefulness has passed. As a matter of fact, the auscultatory index for the diastolic pressure has

[3] Peabody, George L.: Relations between arterial disease and visceral changes. Tran. Assn. Amer. Phys., 1891, VI, 154-178.

[4] Councilman, William T.: On the relations between arterial disease and tissue changes. *Ibid.*, 179-192.

[5] Abel, J. J., and Crawford, A. C.: On the blood pressure raising constituent of the suprarenal capsule. Trans. Assn. Amer. Phys., 1897, XII, 461-480.

[6] Cabot, R. C.: Measurements of blood pressure in fevers before, during and after the administration of strychnin. Trans. Assn. Amer. Phys., 1904, XIX, 22-23.

[7] Stengel, A.: Clinical studies in arteriosclerosis. Trans. Assn. Amer. Phys., 1904, XIX, 512-518.

[8] Stengel, A., and Stanton, W. B.: The heart and circulation in pregnancy and the puerperium. *Ibid.*, 520-553.

[9] Potain: Arch. de phys. norm. et path., 1889, I, 556.

[10] Riva-Rocci, S.: Un nuovo sfigmomanometro. Gazz. med. di Torino, 1896, XLVII, 981, 1001.

[11] Hill, Leonard, and Barnard, Harold: A simple and compact form of sphygmometer or arterial-pressure gauge devised for clinical use. Brit. Med. Jour., 1897, II, 904.

[12] v. Recklinghausen, H.: Ueber Blutdruckmessung beim Menschen. Arch. f. exper. Pathol. u. Pharmakol., 1901, LXVI, 78.

[13] Korotkow: Berichte der kaiserlichen Militärärzlichen Akademie. Petersburg, 1905, XII, 395.

made every instrument employing circular compression of the upper arm available for any clinical use.[14]

From among the many studies, critical and experimental, which have contributed to the perfection of the method, to single out those of conspicuous importance in the development of clinical sphygmomanometry is difficult, and to mention them all quite impossible. In this country the work of Erlanger, of Cook and Briggs, and of Stanton is especially important; in England that of Leonard Hill and his various collaborators, of George Oliver, and more recently of MacWilliam and his co-workers. Gallavardin in France, and in Germany, Hensen and Gumprecht were among the pioneers, and von Recklinghausen and Ottfried Müller have rendered conspicuous service. The monographs dealing with the methods and results of blood pressure study have also been valuable in promoting a widespread use of the instrument.[15]

The only significant factor of error which is still inherent in the bloodless measurement of human arterial pressure is due to the resistance of the arterial wall itself. This was first emphasized by Russell,[16] and was so overemphasized as to call forth experimental investigations, which have now determined its importance.[17]

It is altogether probable that in all normal persons and in the vast majority of patients the resistance offered by the arterial wall to external compression is negligible, but in a few patients with arterial disease such resistance is clearly the cause for overestimation by clinical instruments of the actual blood pressure. As both Gallavardin and MacWilliam have shown, repeated compression of the artery in most of the cases abolishes the local tonus responsible for this error. It is also possible, as MacWilliam has demonstrated and as I have found in my own work, to detect the cases in which this error is important by making both palpatory and auscultatory determinations of the systolic pressure, these patients showing a striking divergence between the two indices. With these exceptions, and the necessary avoidance of excitement and other environmental influences on blood pressure, it is now possible for the clinician to determine with a high degree of accuracy both the maximum or systolic, and the minimum or diastolic, pressure. Thirty years ago only the most approximate measurements of the systolic pressure were possible.

II. Contributions to Diagnosis.

Clinical blood pressure studies have been of greatest value as an aid in diagnosis. Even the earliest and crudest confirmed and greatly extended the older clinical observations on the significance of the high tension pulse in the diagnosis of chronic renal disease. All subsequent studies have emphasized hypertension as a cardinal symptom of chronic Bright's disease—a symptom now more easily detected than any other manifestation of the disease. One has but to turn to Flint's "Practice" to see how completely the sphygmomanometer has revolutionized the diagnosis of this affection. On page 889 the following statement begins the discussion of the diagnosis of chronic Bright's disease: "The diagnosis of chronic as of acute Bright's disease is to be based on the evidence afforded by examination of the urine." Certainly no medical teacher at the present time would regard the urinary findings as the first evidence of this type of renal disease, though recognizing their great importance. The curves from my own blood pressure observations, shown in Charts 1 and 2, strikingly illustrate the diagnostic importance of hypertension in chronic renal disease.

In 1886 the detection of albumin and casts was relatively easy and objective, and the discovery of high blood pressure in many cases difficult and to a large extent dependent upon the special skill of the examiner. At the present day the detection of high blood pressure is absolutely simple and wholly objective, and we have learned how misleading it is to infer from the presence or absence of albumin and casts either the presence or absence of chronic Bright's disease.[18]

With increasing use of the sphygmomanometer all observers

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[14] For full discussion and description of methods see Norris: Blood Pressure, its Clinical Applications, Phila., 1914, p. 63 *et seq.* Also MacWilliam & Melvin: Estimation of Diastolic Blood Pressure, "Heart," 1914, V, 153-196.

[15] The following monographs are worthy of record:

v. Basch, S.: Die Herzkrankheiten bei Arteriosclerose. Berlin, 1901.

Potain, C.: La pression artérielle de l'homme à l'état normal et pathologique. Paris, 1902.

Oliver, G.: Studies in blood pressure, physiological and clinical. Lond., 1902.

Janeway, T. C.: The clinical study of blood pressure. New York, 1904.

Pal, J.: Gefässkrisen. Leipz., 1905.

Müller, O.: Der arterielle Blutdruck und seine Messung beim Menschen. Ergeb. d. inn. Med. u. Kinderheilk., 1908, II, 367-417.

Gallavardin, L.: La tension artérielle en clinique. Paris, 1910.

Horner, A.: Der Blutdruck des Menschen. Leipz., 1913.

Norris, G. W.: Blood pressure: its clinical applications. Phila., 1914.

A full literature will be found in these monographs.

[16] Russell, W.: Arterial hypertonus, sclerosis and blood pressure. Edinb. and Lond., 1908, p. 87.

[17] Since the study presented by Park and myself before this association in 1910 (An experimental study of the resistance to compression of the arterial wall. Arch. Int. Med., 1910, VI, 586), the following important publications have appeared:

Gallavardin, L. and Haour, J.: Baisse systolique de la tension artérielle au moment de la mensuration. Arch. d. mal. du cœur, 1912, V, 81.

MacWilliam, J. A. and Kesson, J. E.: The estimation of systolic blood pressure in man with special reference to the influence of the arterial wall. "Heart," 1913, IV, 279.

MacWilliam, J. A., Kesson, J. E. and Melvin, S.: The conduction of the pulse wave and its relation to the estimation of systolic blood pressure. *Ibid.*, 393.

Hill, L. and Flack, M.: The effect of lability (resilience) of the arterial wall on the blood pressure and pulse curves. Proc. Roy. Soc. Lond., 1913, LXXXVI, s. B., 365.

Wells, S. R. and Hill, L.: The influence of the resilience of the arterial wall on the blood pressure and on the pulse curve. *Ibid.*, 180.

[18] Statistical data on this point will be found in my paper, "A Clinical Study of Hypertensive Cardiovascular Disease." Arch. Int. Med., 1913, XII, 755. Also Trans. Assn. Amer. Phys., 1913, XXVIII, 333.

began to encounter patients with hypertension without the urinary evidences of nephritis and without renal symptoms. Such patients had previously been supposed to suffer from idiopathic hypertrophy of the heart. The opinion has gradually developed that a symptom-complex exists in which the symptom first in importance and in time of development is increased arterial pressure. Patients presenting this symptom-complex suffer, as a rule, from minor grades of myocardial insufficiency or from cerebral symptoms, or present an indefinite neurasthenic state. Evidences of renal insufficiency are conspicuously absent during the earlier stages. The condition has been given various names—latent *angiosclerosis* by von Basch, *presclerosis* by Huchard, *hyperpiesis* by Allbutt. I have preferred to call it *primary hypertensive cardiovascular*

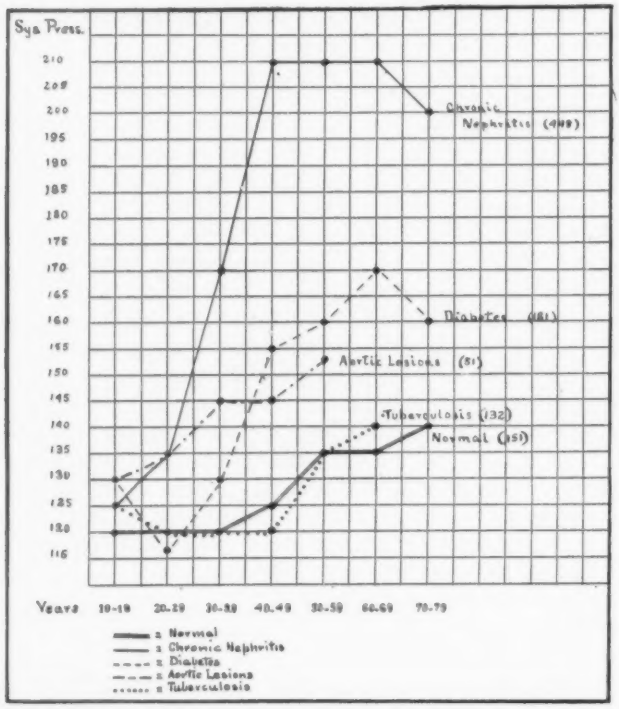

CHART 1.—Median systolic blood pressures, arranged by age periods. Personal observations. (Figures in brackets at right of curves indicate total number of individuals observed in each group.)

disease. It is often spoken of merely as *hypertension* or *essential hypertension,* and has recently been designated *benign essential hypertension* by Volhard and Fahr.[19] It has therefore neither a uniformly accepted name nor a universally accepted interpretation, but is everywhere recognized as one of the commonest types of circulatory disease. This recognition is due entirely to the sphygmomanometer.

Those who dislike terms which express a functional and not an anatomical diagnosis have included these cases either in the category of chronic nephritis or of arteriosclerosis. The careful study of the blood pressure in each of these conditions, however, does not warrant the view that the continued existence of the symptom hypertension is in itself sufficient ground for the diagnosis of one or the other of them in the sense in which the terms are ordinarily used. I have already discussed this at length elsewhere.[20] Suffice it to say here that all observers agree that widespread sclerosis of the accessible peripheral arteries or of the aorta may exist with normal or low blood pressure. Therefore hypertension is not a necessary sequence of ordinary arteriosclerosis. On the other hand, while the study by finer methods of the kidneys of such patients as die has shown that in almost all of them some changes in the smaller renal vessels and in the glomeruli can be made out,[21] nevertheless there is no parallelism whatever between the extent of the kidney lesions and the height of the blood pres-

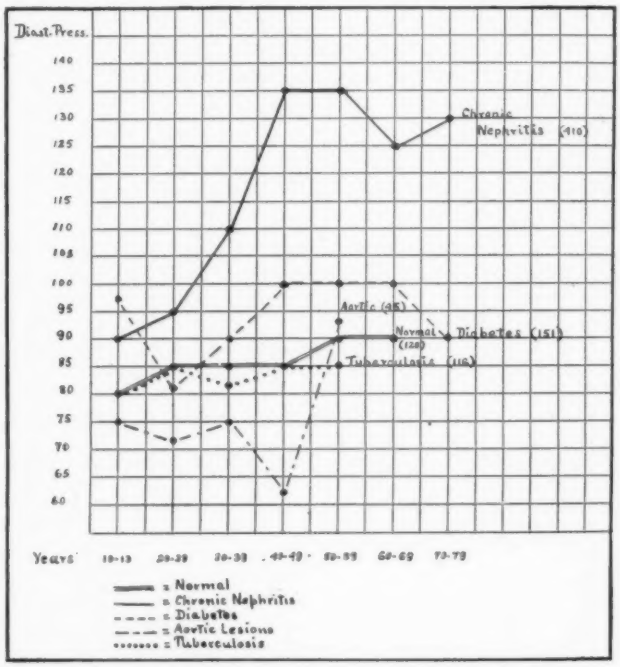

CHART 2.—Median diastolic blood pressures, arranged by age periods. Personal observations. (Figures in brackets at right of curves indicate total number of individuals observed in each group.)

sure. In the end-stages these patients may certainly exhibit the anatomical picture of the primary contracted kidney. In the early stages, however, as Jores has so clearly pointed out,[22] the kidney is only one of the organs implicated in the wide-

[19] Volhard, F. and Fahr, Th.: Die Brightsche Nierenkrankheit. Berlin, 1914.

[20] Janeway, T. C.: Nephritic hypertension; clinical and experimental studies. Amer. Jour. Med. Sci., 1913, CXLV, 625.

[21] Fischer, J.: Ueber die Beziehungen zwischen anhaltender Blutdrucksteigerung und Nierenerkrankung. Deutsch. Arch. f. klin. Med., 1913, CIX, 469.

[22] Jores, L.: Ueber die Arteriosklerose der kleinen Organarterien und ihre Beziehungen zur Nephritis. Virchows Arch., 1904, CLXXVIII, 367.

spread disease of the arterioles, and may show but little change. To consider essential hypertension, therefore, wholly of renal origin is unwarrantable at the present time; and a functional designation may be wisely retained, unless the term "arteriolar sclerosis" can find acceptance.

The foregoing condition occurs frequently after middle life, but is peculiarly common in elderly diabetics (see Charts 1 and 2). On the other hand, it is clear from my own observations and those of Elliott[22] that diabetes itself is without influence on the arterial pressure. Hypertension is therefore presumably an expression of the well-known tendency of diabetics of suitable age to develop arterial disease; or possibly in some cases arterial disease is the cause of the lesions responsible for the diabetes.

In the differential diagnosis of the type of existent renal disease blood pressure observation plays a conspicuous part. Great stress has been laid upon this by Volhard and Fahr in their recent monograph.[24] Without going quite to the same length of schematic differentiation, it can be said that, in patients presenting the other evidences of kidney disease, increased blood pressure always suggests either primary disease of the vessels or true diffuse nephritis. As I have seen hypertension develop during the early anuria of necrosis of the kidney from bichloride of mercury, however, I do not believe, as they do, that it can be considered as absolutely differentiating between the degenerative nephroses on the one hand and the inflammatory nephritides and vascular scleroses on the other. A persistently subnormal blood pressure in a patient with renal symptoms is certainly the strongest evidence of amyloid kidney. In clinical acute Bright's disease hypertension regularly indicates a true diffuse nephritis or a severe renal insufficiency.

Of less diagnostic value, but still a real contribution to clinical medicine, has been the study of blood pressure in increased intracranial tension. This has been thoroughly elucidated by animal experimentation. In the differential diagnosis of coma, hypertension always suggests cerebral hæmorrhage acting in this way, or uremia associated with a pre-existing hypertensive nephritis.

Transient hypertension has been exhaustively studied by Pal.[25] Of the so-called vascular crises which we have learned to recognize, that accompanying puerperal eclampsia is the most important. Blood pressure studies have strikingly confirmed the early observations of Vaquez[26] that a persistent hypertension after the delivery of the child points to eclampsia as probable. Similarly, hypertension has been shown to accompany lead colic and the gastric crises of tabes, and has some diagnostic value in cases of obscure abdominal pain. Exophthalmic goitre is associated with moderate elevation of blood pressure in a large proportion of cases.

In the diagnosis of the other forms of circulatory disease, blood pressure studies have yielded little of importance. Normal blood pressure in a patient with myocardial insufficiency without valvular disease helps materially toward the diagnosis of primary disease of the myocardium. It is a striking fact, however, as Starling[27] and others have shown, that a moderate hypertension commonly accompanies myocardial insufficiency, the pressure falling as the circulation improves.

In the study of the valvular diseases of the heart, blood pressure observation has proved valuable only in the diagnosis of aortic regurgitation. This is facilitated in two ways; first, by the demonstration of the increased pulse pressure in those cases which do not show a typical collapsing pulse (see Charts 1 and 2), and second, by the very interesting finding, first made by Hill and Flack,[28] that the systolic blood pressure in the leg in aortic regurgitation is regularly higher than in the arm—sometimes to an astonishing extent. I am personally convinced of the diagnostic value of this discrepancy between arm and leg pressures, which does not seem to be found in other pathological conditions or in normal individuals when due precautions are taken.

As an aid to clinical diagnosis subnormal blood pressure has been of relatively little value. While it commonly accompanies the infectious diseases and cachectic states, it is but one of many symptoms and the diagnosis does not depend upon its discovery. In the recognition of amyloid disease and of Addison's disease, however, a persistently low blood pressure is of very real importance. In the detection of internal hemorrhage the discovery of a falling arterial pressure, and especially of a falling pulse pressure and pulse rate, as described by Wiggers,[29] may be significant. A fall in pressure during pleural aspiration has been shown by Capps and Lewis[30] to be an indication of reflex inhibition of the heart or vasomotor center. The relation of low blood pressure to surgical shock, while of great value to the surgeon, is beyond the limits of this paper.

The early investigators of blood pressure, especially in

[22] Elliott, A. R.: A clinical study of blood pressure variations in diabetes and their bearing on the cardiac complications. Jour. Amer. Med. Assn., 1907, XLIX, 27.

[24] Volhard, F. and Fahr, Th.: Die Brightsche Nierenkrankheit. Berlin, 1914.

[25] Pal, J.: Gefässkrisen. Leipzig, 1905.

[26] Vaquez and Nobécourt: De la pression artérielle dans l'éclampsie puerpérale. Bull. et mém. Soc. méd. d. hôp. de Paris, 1897, XIV, 117.

[27] Starling, H. J.: Observations on the arterial blood pressure in heart disease. Lancet, 1906, II, 846.

[28] Hill, L. and Flack, M.: The accuracy of the obliteration method of measuring arterial pressure in man. Proc. Physiol. Soc., Lond., 1908-9, p. 48.

These observations have been confirmed by Hare (The Difference between Systolic Pressure in the Arm and in the Leg in Aortic Regurgitation. Trans. Assn. Amer. Phys., 1910, XXV, 91), by Hill and Rowlands (Systolic Blood Pressure in Cases of Aortic Regurgitation. "Heart," 1912, III, 219), by Rolleston (On the Systolic Blood Pressure in the Arm and Leg in Aortic Incompetence. *Ibid.*, 1912, IV, 83) and by Murray (Systolic and Diastolic Blood Pressure in Aortic Regurgitation. Brit. Med. Jour., 1914, 697).

[29] Wiggers, C. J.: The prognostic significance of pulse-pressure changes during hæmorrhage. Arch. Int. Med., 1910, VI, 281.

[30] Capps, J. A. and Lewis, D. D.: Blood pressure lowering reflexes from irrigation of the chest in emphysema. Trans. Assn. Amer. Phys., 1909, XXIII, 188.

France, beginning with Marfan,[31] believed low blood pressure to be an important indication of tuberculosis. Norris[32] still states that tuberculosis is generally associated with hypotension. My own observations have convinced me that as a factor in the diagnosis of tuberculosis blood pressure measurements have no real value. A glance at the curves in the accompanying charts (Charts 1 and 2) shows in striking fashion the essential correspondence of the curve of the normal and the curve of the tuberculous individuals, as observed in an office practice. Shalet,[33] who has examined about 1000 patients at the Otisville Sanatorium, has come to the same conclusion. It is of course unquestionable that in advanced and febrile tuberculosis a low blood pressure exists and has the same significance as in other active infections.

Is there a state of constitutional or essential hypotension, as there is of essential hypertension, as has been held by Bishop and a few other observers?[34] At the present time I am not convinced of this, for I have personally observed systolic pressures which would ordinarily be considered subnormal—below 110 in men and 95 to 100 in women—existing over long periods of absolutely perfect health and physical activity. Low blood pressure, in the cases to which the term "constitutional low blood pressure" has been applied, is merely one symptom of lowered tone of the central nervous system—though possibly an important one to recognize.

For the final determination of the importance of slight deviations from the average blood pressure in normal individuals a knowledge of the limits of normal variation is essential. Its attainment necessitates a vast number of observations and has therefore taken much longer than the acquisition of a knowledge of the more marked pathological changes in pressure. The real basis has been afforded by the introduction of the sphygmomanometer in life insurance examinations. Since the publication by Fisher[35] of the blood pressure records of 19,339 accepted candidates for life insurance, all previous tabulations of average pressures in normal adults can be discarded as inadequate. Fisher's table follows:

Ages	Number	Average Blood Pressure
15-20	281	119.85
21-25	785	122.76
26-30	791	123.65
31-35	689	123.74
36-40	2,111	126.96
41-45	6,740	128.56
46-50	4,471	130.57
51-55	2,371	132.13
56-60	1,100	134.78
Totals	19,339	128.91

Dr. Fisher has written me personally that since this publication he has been informed of a record of 9000 readings by another company which did not vary one millimeter in the average of any age from those he has tabulated—making an average standard based upon the observation of over 28,000 healthy adults. However, for the decision that a particular blood pressure reading is beyond the possible normal it is necessary to know not only the normal average but the limits of variation at any age. This must be so much a matter of opinion as to the health of the individual showing a debatable abnormal blood pressure that there will always be a difference of opinion about it. I am inclined to revise my former opinion and to agree with Cook,[36] and Lauder Brunton before him, that over 135 mm. up to middle life, and 145 or 150 mm. thereafter, should be regarded as pathological hypertension if found on repeated examinations. For the lower limits of normal pressure in adults I should take 100 mm. in women and 105 to 110 in men, though attaching less significance to occasional readings slightly below this.

The diastolic pressure is unquestionably of great importance, and in the determination of abnormally high or low blood pressure should have equal consideration, but it is as yet so little used that a consideration of it would go beyond the scope of the present paper (see Chart 2).

The tabulation of my personal blood pressure readings in persons without detectable disease, as shown in Charts 1 and 2, is interesting as showing how closely a comparatively small series of observations may follow the averages obtained in such a large series as Fisher's. Of course, the smaller the series the less smooth the curve, but the figures are strikingly similar.

All figures for the normal individual bring out clearly the definite tendency of the blood pressure to increase with advancing years. The effect of age, however, is most strikingly seen in childhood, and within recent years a large number of important studies on blood pressure in children has been published.[37] In this particular field of study the oscillatory method—which I believe gives erroneous results in adults—has found a special application, because neither the palpatory nor the auditory

[31] Marfan, B. J. A.: De l'abaissement de la tension artérielle dans la phthisie pulmonaire. Compt. rend. Soc. de biol., Par., 1891, III, 346.

La tension artérielle dans la tuberculose pulmonaire chronique et son importance pour le pronostic. Rev. d. méd., 1907, XXVII, 1005.

[32] Norris, G. W.: Blood pressure; its clinical applications. Phila., 1914, p. 199.

[33] Shalet, L.: Blood pressure in pulmonary tuberculosis. New York State Jour. Med., 1914, XIV, 189.

[34] Bishop, L. F.: Constitutional low arterial tension in children. Ann. Gynec. and Pediat., 1906, XIX, 85. Also Jour. Amer. Med. Assn., 1906, XLVII, 1734. Constitutional low arterial tension and its relation to the life of the individual. New York Med. Jour., 1906, LXXXIII, 967.

Goodman, E. H.: Some cases of hypotension associated with a definite symptomatology. Amer. Jour. Med. Sci., 1914, CXLVII, 503.

Norris, G. W.: Blood pressure: its clinical applications, Chap. VI. Essential hypotension (constitutional low arterial pressure).

[35] Fisher, J. W.: The diagnostic value of the sphygmomanometer in examinations for life insurance. Jour. Amer. Med. Assn., 1914, LXIII, 1752.

[36] Cook, H. W.: Blood pressure in prognosis. Med. Rec., 1911, LXXX, 959.

[37] Durand-Viel, P.: Des variations de la pression artérielle au cours de quelques maladies chez les enfants. Paris, 1903.

Stone, J. S.: Report on blood-pressure determinations made at

index of blood pressure can be readily used in very small children. The accompanying chart (Chart 3) from Koessler's article shows very clearly the rapid rise of pressure during the growth period of the child. In using it for absolute values, however, one must remember that the oscillometric method gives an overestimation of the systolic pressure. The majority of those who have studied this aspect of the question agree with Wolfensohn-Kriss, that the chief parallelism of the blood pressure in childhood is with the increasing height and body weight rather than with age itself, and that the slightly lower pressure seen in girls and in women, when compared with males of the same ages, is related to the lesser height and weight rather than to sex itself.

An interesting study has been made by Wildt[28] of blood pressure in the aged. He found the following average blood pressures:

Ages	Systolic	Diastolic
60-64	137	76
65-69	143	78
70-74	148	80
75-79	152	82
80-84	148	78
85-89	162	85
90-96	129	59

These averages represent readings on 250 individuals, without the exclusion of those who showed circulatory or other disease. The percentages showing marked hypertension in this group were as follows:

Ages	Systolic Pressures Over 150	Over 200
65-69	49%	3%
70-74	44%	6%
75-79	39%	7%
80-84	38%	12%
85-89	64%	14%

These pressures were quite regularly associated with chronic nephritis or arteriosclerosis. Hypotension he found only in tuberculosis and pneumonia, in six cases of contracted kidney and in individuals with weak hearts. There was a regular tendency for the amplitude or pulse pressure to increase, the diastolic pressure frequently being lower than in earlier life.

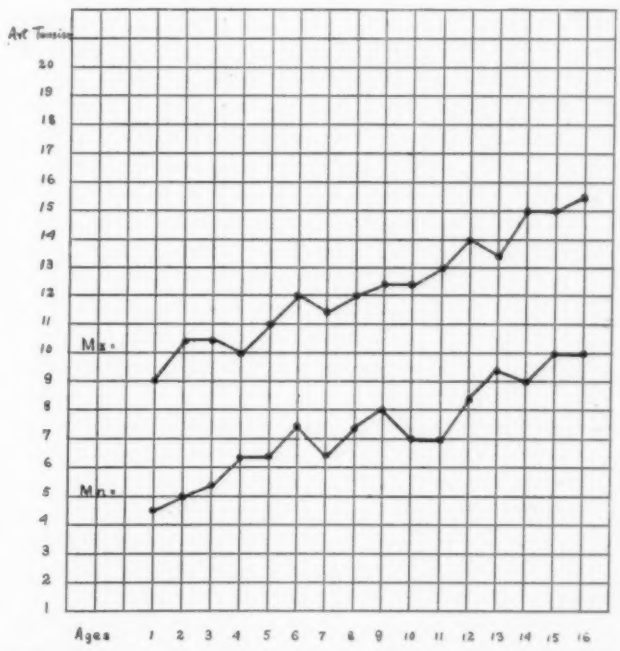

CHART 3.—Curve of pressures arranged by ages (boys), from "L'Oscillométrie appliquée à l'étude de la tension artérielle chez les enfants," L. Koessler, Paris, 1912, p. 65.

It is interesting that in the four individuals above ninety the pressure was much lower than at the preceding age periods.

An important observation on blood pressure in the normal adult male has been made by Chamberlain[29] in the Philippines, showing, from the examination of 992 American soldiers, that the average pressures in the tropics are lower than the normal averages for temperate climates and that the pressure was lower during the first three months of tropical residence than

the Boston Children's Hospital. Div. Surg., Harvard Med. School, 1903-4, I, Bull. No. II, 18.

Trumpp, J.: Blutdruckmessungen an gesunden und kranken Saüglingen. Jahrb. f. Kinderh., 1906, LXII, 43.

Gaujoux, E.: Recherches sur la tension artérielle normale chez les enfants. Ann. de méd. et chir. inf., 1908, XII, 435.

Stowell, W. L.: Blood pressure in children. Arch. Pediat., 1908, XXV, 88.

Kaupe, W.: Der Blutdruck im Kindesalter. Monatsch. f. Kinderh., 1910, IX, 257.

Seiler, F.: Praktische Bemerkungen über den Blutdruck und über Normalwerte des Blutdruckes im Kindesalter. Cor.-Bl. f. Schweiz. Aerzte, 1910, XL, 433.

Wolfensohn-Kriss, P.: Ueber den Blutdruck im Kindesalter. Arch. f. Kinderh., 1910, LIII, 332.

Salle, V.: Ueber Blutdruck im Kindesalter. Jahrb. f. Kinderh., 1911, LXXIII, 273.

Jarricot: Mesure de la tension artérielle chez les enfants et oscillomètre de Pachon comme sphygmo-signal. Péd. prat., 1912, X, 392.

Koessler, L.: L'oscillimétrie appliquée à l'étude de la tension artérielle chez les enfants. Paris, 1912, No. 144.

Balard, P.: Le pouls et la tension artérielle de l'enfant et du nouveau-né. Gaz. des hôp., Paris, 1913, LXXXVI, 837.

Friberger, R.: Ueber die Entwicklung von Puls und Blutdruck im späteren Kindesalter. Arch. f. Kinderh., 1913, LX, 331.

Katzenberger, A.: Puls und Blutdruck bei gesunden Kinder. Kinderh., 1910, IX, 257.

Leitao, M.: Pression artérielle chez l'enfant. Arch. d. méd. d. enf., 1913, XVI, 102.

Judson, C. F. and Nicholson, P.: Blood pressure in normal children. Amer. Jour. Dis. Children, 1914, XII, 257.

[28] Wildt, H.: Ueber Blutdruck im Greisenalter. Zentralbl. f. Herzkrankh. u. Gefässkrankh., 1912, IV, 41.

[29] Chamberlain, W. P.: A study of the systolic blood pressure and the pulse rate of healthy adult males in the Philippines. Phil. Jour. Sci., 1911, VI, 467.

subsequently, and on the average about 3 to 5 mm. lower during the hottest season of the year. His table is as follows:

Ages	Number	Average Blood Pressure
18-20	36	115
20-25	469	114.3
25-30	286	115.9
30-35	109	116.7
35-40	58	120.5
Over 40	34	119.6

He failed to find any marked parallelism between blood pressure and the height and weight of the individual. The mean pressure of Philippinos during the same age periods did not differ from that of Americans.

III. Contributions to Prognosis.

So far, the most important application of blood pressure measurements to the solution of prognostic problems has been made by the life insurance companies. This is quite natural, since the entire business of life insurance is based upon scientific prognosis. Only recently, however, have actuaries attempted to make statistical studies of prognosis in disease, and the results of this application of statistics, on a scale sufficiently large to reduce the influence of individual error and variation to a negligible quantity, are of great importance to the medical profession. Physicians rarely have the opportunity to observe hypertensive patients until they develop symptoms, whereas the life insurance examiner has the opportunity to detect these conditions before any other evidence of deviation from the normal exists. During the years from 1907 to 1910, the company of which Dr. Fisher is medical director accepted 2,661 applicants, with an average blood pressure of 142.43, between the ages of 40 and 60, and their average mortality was practically the mortality of all of the insured. During the same period the company accepted 525 persons with an average pressure of 152.58, or only 10 mm. above the average of accepted risks. These persons showed a mortality 30% above the general average of the company. They rejected 1,970 applicants with an average pressure of 161.44 between the years 1907 and 1913, and, when followed up, these have shown a mortality more than double the average for the company—and this is probably below the facts, because of incomplete returns.[39]

These figures are eloquent testimony to the value of the instrumental measurement of blood pressure in the early recognition of what is frequently the sole evidence of a deviation from the normal in middle-aged persons. Fisher states that but little value is attached as yet to their observations of low pressure.

Apart from the general indication which hypertension gives of the eventual probability of the development of symptoms of myocardial insufficiency, renal insufficiency or cerebral vascular disease, the study of blood pressure has not yet led to important gains in the ability to predict duration of life. In particular, it is clearly a mistake, as I have emphasized in a previous report before this association,[40] to assume that an individual with extreme hypertension will die sooner than one with a moderate elevation of blood pressure. The blood pressure reading is an additional factor to be combined by the physician with all the other symptoms and signs presented by the patient in arriving at that most difficult of practical judgments, a prognosis as to the duration of life. Rapidly falling blood pressure is a frequent terminal symptom in hypertensive patients dying of uræmia, and, as in apoplexy, is a very bad omen. I have also found a steady rise in pressure to be a serious feature in cases of chronic diffuse nephritis, usually indicating the development of severe renal insufficiency.

In the early days of blood pressure study I, like most physicians interested in this field, hoped that it would furnish most important indications in acute infectious disease. That hope has been disappointed. I think that most of us must now agree with the conclusions of Kurt Weigert [41] from his extensive studies of the various acute infections, and which have been confirmed, for scarlet fever, by Rolleston,[42] that the value of the blood pressure measurement for prognosis in the acute infectious diseases is slight. It is an additional factor which is occasionally useful, as in typhoid patients with hemorrhage; but for the most part the simpler observations made by our predecessors in clinical medicine, of the facies, the tongue, the pulse, the heart sounds and the state of the nervous system make the prognosis equally well without a knowledge of the blood pressure curve. That further observations may permit of greater refinement in this field is not to be denied.

In one disease—lobar pneumonia—so good an observer as Gibson [43] thought he had discovered a most important prognostic indication in the relation of blood pressure and pulse rate, which has become known as Gibson's rule. The rule is that, when the blood pressure, expressed in millimeters of mercury, falls below the pulse rate per minute, expressed in figures, the prognosis is unfavorable. But a recent critical study by Newburgh and Minot [44] has shown that the prognostic inferences based on Gibson's rule were oftener wrong than right in their 15 cases. They emphasize the fact that low systolic pressures are not "invariably of evil omen," and in this I heartily concur.

IV. Contributions to Therapeutics.

In the progress of practical medicine, advances in the diagnosis of disease have usually preceded advances in therapeutics, often by a very long period. In the treatment of diseases

[39] Janeway, T. C.: A clinical study of hypertensive cardiovascular disease. Arch. Int. Med., 1913, XII, 755. Also Trans. Assn. Amer. Phys., 1913, XXVIII, 333.

[41] Weigert, K.: Ueber das Verhalten des arteriellen Blutdrucks bei den akuten Infektionskrankheiten. Samm. klin. Vortr., 1907, No. 459 (Inn. Med., No. 138, 65).

[42] Rolleston, J. D.: Blood pressure in scarlet fever. Brit. Jour. Child. Dis., 1912, IX, 444.

[43] Gibson, G. A.: Some lessons from the study of arterial pressure. Edinburgh Med. Jour., 1908. n. s., XXIII, 17.

[44] Newburgh, L. H., and Minot, G. R.: The blood pressure in pneumonia. Arch. Int. Med., 1914, XVI, 48.

associated with high blood pressure the ability to detect hypertension led at first to widespread abuse of vaso-dilators. Further study, however, clearly showed both the difficulty of permanently lowering the blood pressure by drugs and the occasional harm produced in these patients by successful vaso-dilatation; and, as a result, the treatment of essential hypertension today is the treatment of the patient and not of the hypertension—safe-guarding treatment in the strictest sense—the endeavor is to avoid myocardial or renal insufficiency, or a vascular accident, and to limit the operation of known causes for hypertension.

The most remarkable claims for the therapeutic control of hypertension have been made by physicians employing the so-called "d'Arsonvalization," a special form of high frequency current. A critical study of this whole literature has been to me far from convincing. A vast majority of the publications have been by Moutier. He has used very inaccurate instruments for the measurement of blood pressure. In his most important account of 50 cases treated,[45] in 43 the fall in pressure could have been explained by the well-known tendency for first readings to be higher than subsequent ones, and could be duplicated from my records of untreated cases. Of his remaining seven cases, in only five was there any reduction in pressure which could be considered at all permanent, and in not a single case was there any fore-period of observation to determine the spontaneous variations, which, in hypertensive patients, may assume considerable proportions.

A study of 266 cases of arteriosclerosis by Bühler[46] is on its face rather more convincing. The few patients in whom I have been able personally to control the effects of this treatment, unknown to the physician who was administering it, have shown no result whatever, although a marked effect was claimed by the electro-therapeutist. The whole subject, however, is deserving of scientific and objective investigation."

Until the real mechanism by which high blood pressure is produced shall be thoroughly understood, neither preventive nor curative treatment can be developed. The use of the sphygmomanometer has, however, contributed largely to the more careful study of these patients, and thus indirectly to their more intelligent treatment. It affords a means of gauging objectively the necessary dose of a vaso-dilator when one must be used—and incidentally has given proof of the inertness of many of the preparations of vaso-dilating drugs upon the market. Thus blood pressure studies, from the standpoint of therapeutics, have been largely critical and negative.

They have been of great importance in respect to one drug, digitalis. That digitalis—a pharmacological action of which in the intact animal is to produce marked vaso-constriction—does not tend uniformly to raise the blood pressure in hypertensive patients with myocardial insufficiency, or, if it does, improves the circulation at the same time, has been especially emphasized by Sahli,[48] and has gradually become common knowledge.[49] This is a matter of the first importance, because we have no substitute for the digitalis bodies in myocardial insufficiency.

Control by the sphygmomanometer of the so-called cardiac or circulatory stimulants has shown how misplaced has been the faith of physicians in such drugs as strychnine and caffein as a means of combating circulatory failure in acute infectious diseases or in surgical shock.[50] The various hydrotherapeutic procedures have been studied in the same way, and a large literature is growing up on the subject.

In the treatment of acute infectious disease I think we must still agree with Weigert[47] that knowledge of the blood pressure does not help us, though this may be because of inadequate development of the methods for measuring the pulse pressure. It is possible that a very careful critical study of systolic, diastolic and pulse pressures may give the observation of the arterial pressure a greater importance in acute diseases than it possesses today.

V. Contributions Toward a Functional Pathology of the Circulation.

In my opinion the clinical study of blood pressure during the past 30 years has justified the time devoted to it, as much by its contribution to medical theory as by its contribution to medical practice. Prevention of disease must always depend upon a knowledge of causation and transmission, and its adequate treatment upon a complete understanding of the mode of production of the lesions and the symptoms which together constitute the phenomena of disease. The problem of the etiology of the chronic so-called degenerative diseases is is one of the greatest awaiting solution at the present day, and the first approach to it must be from the standpoint of accurate clinical observation. Clinical medicine, not animal experimentation, determines and defines the problem.

The accurate measurement of the blood pressure in patients with cardiovascular disease has afforded a mass of incontrovertible facts, which are essential for the attainment of a sound functional pathology of the circulatory system. Increased blood pressure has been found to be the earliest and the most important functional disturbance in a very common type of circulatory disease. Its association with certain lesions of the

[45] Moutier, A. and Challamel, A.: Sur 50 nouveaux cas d'hypertension artérielle permanente traités par la d'arsonvalization. Ann. d'électrobiol., 1904, VII, 657. Also Rev. d. mal de la nutrition, 1905, III, 82.

[46] Bühler, A.: Erfolge der Hochfrequenzströme bei Arteriosklerose. Med. Klin., 1914, X, 55.

[47] For further literature on therapeutics in hypertension see Norris: "Blood Pressure: Its Clinical Application," Chap. XIII, p. 273.

[48] Sahli, H.: Ueber Herzmittel und Vaso-motorenemittel. Kong. f. inn. Med. Verhandl., 1901, XIX, 45.

[49] Martinet, A.: Pressions artérielles et viscosité sanguine. Paris, 1912.

Lawrence, C. H.: The effect of digitalis on the blood pressure and pulse pressure in the presence of cardiac decompensation. Boston Med. & Surg. Jour., 1914, CLXX, 37.

Janeway, T. C.: The comparative value of cardiac remedies. Arch. Int. Med., 1914, XIII, 361.

[50] Newburgh, L. H.: The use of strychnine and caffein as cardiovascular stimulants in the acute infectious diseases. Arch. Int. Med., 1915, XV, 458.

Crile, G. H.: Blood pressure in surgery. Phila., 1903.

arteries, in the kidneys and elsewhere, has been determined. Its development has been traced in other cases where obvious renal disease has preexisted. In a considerable number of cases the evidence strongly suggests that the increased arterial pressure develops parallel with changes in the arteries rather than as their sequel. Many associations of temporarily high blood pressure with intoxications and other abnormal conditions have been discovered. In addition, the effects of myocardial insufficiency, of acute infections, and of other complicating disturbances in lowering a persistent hypertension are being worked out in greater and greater detail. Accessory hypertensive influences are being similarly described with greater completeness. The problem of the cause of the hypertrophied heart in chronic Bright's disease engrossed the generation preceding ours. For us it has become the problem of the cause and the pathological physiology of permanent hypertension. This is more than a change in emphasis. It means an accumulation of exact knowledge derived from clinical observation by a physiological method which has already enlarged our understanding of a pathological process, of which the lesion in the heart is an end result, and has brought the problem one step nearer solution.

In spite of the considerable advance in our knowledge of the modes of production of hypertension in animals and the remarkable discoveries concerning the action of the adrenals and other ductless glands, the problem of the causation of hypertension still awaits solution. The clinical observation of blood pressure by family practitioners over a long period of years, now that the sphygmomanometer has become a routine instrument, may yet contribute data of importance toward this much desired end.

From a purely negative standpoint the discovery that myocardial insufficiency, as in valvular diseases of the heart, results in a great reduction in the arterial blood mass but not in arterial blood pressure, while at first sight disappointing to physicians seeking only aid in the immediate practical problems of medicine, is an important fact in circulatory pathology. It shows the presence of a compensatory vasomotor mechanism in cardiac disease. In states of supposed circulatory collapse in acute infectious disease the same disappointment has been met with. The sphygmomanometer has failed to reveal the expected extreme hypotension until the agonal period. But the sphygmomanometer has given us facts in place of inferences from crude methods. Similarly, graphic and electrical methods are refining the analysis of the cardiac rhythms. From these facts, when combined with like accurate observations by other physiological methods, there will yet be constructed a functional pathology of the circulation which will be the basis for the successful treatment of patients with circulatory disease.

ELUSIVE MOBILITY OF THE BREAST IN A CASE OF RETRO-MAMMARY CYST.

By W. S. Halsted, M. D.

Surgical No. 36,939. Large healthy woman, æt. 43. Admitted to The Johns Hopkins Hospital, May 4, 1915.

About four weeks before admission the patient noticed, quite accidentally, on palpation, an abnormal hardness in the upper half of the right breast. She could not recall having had the slighest pain in either mammary gland.

Examination.—Both breasts were rather voluminous, the right slightly larger than the left. On inspection there was a faint suggestion of fulness about the middle of the upper hemisphere of the right mamma. On palpation a fairly well defined area of induration, measuring approximately 9 x 7 cm., was found. The lower margin of the mass corresponded quite accurately to the horizontal nipple-line. The tumor was very hard and seemed to be inelastic. There was no retraction of the nipple, no evidence of shortening of the subcutaneous trabeculæ on widest excursions of the breast and, in brief, none of the signs of carcinoma. Glandular tissue of considerable thickness apparently intervened between the skin and the hard mass, the margins of which seemed finely roseate.

There was, however, one remarkable manifestation. Several times in the course of the examination, at the moments when the tumor's elasticity was being tested by the exercise of particularly firm pressure, the breast, suddenly, would make an elusive glide outwards under my fingers. This was so surprising that I commented on it to my assistants. At the final examination, on the operating table the same thing occurred, and my associate, Dr. Heuer, who assisted at the operation, remarked that he, too, had been surprised while making his examination to note this abnormal slipping of the breast on the chest wall. As a possible explanation of the phenomenon I suggested retro-mammary cyst. This the tumor proved to be.

Glandular tissue, a centimeter or more in thickness, was cut through before the cyst was punctured. The posterior wall of the cyst was very thin, perhaps one quarter of a millimeter thick, and protruded hernia-like from the under surface of the breast. The precise size and shape of the projecting part of the evacuated cyst could not well be determined. We surmised that it had been hemispherical in shape and about the size of an English walnut.

As lesser grades of this significant motion would probably be overlooked, its manifestation may prove to be not so very uncommon in cases of retro-mammary cyst.

Solid tumors projecting from the under-surface of the breast might, conceivably, in the absence of adhesions or exudative reaction give the same, roller-like glide.

A CASE OF FOOT-AND-MOUTH DISEASE IN MAN.

By PAUL W. CLOUGH, M. D., Baltimore.

(From the Medical Clinic of The Johns Hopkins Hospital.)

The recent appearance of foot-and-mouth disease among cattle and hogs in this country is a matter of importance to physicians as well as to veterinarians, since the disease is occasionally transmitted from animals to man. As its appearance hitherto has been rare in the United States, and as the possibility of human infection has not generally been realized in this country, it seems desirable to put on record a description of a moderately severe typical case of the disease from the medical clinic of The Johns Hopkins Hospital. While it is not the intention to discuss in detail the epidemiology or the symptomatology, a brief outline of what has been learned from a study of the disease in animals is necessary for a clear understanding of its appearance in man.

For more than three centuries foot-and-mouth disease has been known in continental Europe, especially in Germany, Austria, Russia and the Balkans. It occurs in severe epizootics at intervals of from four to six years, causing heavy financial losses. During such an outbreak in Europe in 1911, in Germany alone cases were officially reported in approximately 3,300,000 cattle, 1,600,000 sheep, 2,500,000 hogs and 50,000 goats—about one-seventh of all the susceptible animals in the country.[1] In the intervals between the severe epizootics smaller numbers of sporadic cases occur. The United States has been relatively free from the disease. There was an extensive outbreak in 1870, and limited ones in 1880, 1884, 1902 and 1908. During the past year it has again appeared and has prevailed throughout most of the eastern states.

Of the domestic animals cattle are most susceptible to the disease.[2] Hogs, sheep and goats are somewhat less so. Much more rarely horses, dogs and cats are affected, and occasionally man. Rabbits, guinea-pigs and birds are only rarely infected, even by inoculation. Among susceptible animals the disease is highly contagious, attacking a large proportion of those exposed. In cattle the morbidity rate is often 40% and in some epidemics it has even been 95%.[2] Infection may be by direct contact, but it is most often indirect, by means of contaminated hay or bedding, stalls, common drinking-troughs, or pastures. Infected stock cars and stockyards play a very important rôle in disseminating the disease. Contaminated milk is a prolific source of infection in young animals.

The virus is present in the fluid of the vesicles wherever they occur. Susceptible animals, especially calves, may quite regularly be infected by applying fluid from a vesicle to an abraded mucous membrane or to the abraded skin of the foot or udder. This furnishes a reliable, though expensive method for the experimental study of the disease. The fluid of the vesicle contains the virus in high concentration, 0.0002 cc. often sufficing to infect a calf.[3] It is present in the saliva, feces, urine or milk, whenever these secretions become contaminated with fluid from a ruptured vesicle.[2] After the healing of the ulcers which form when the vesicles rupture the contagion usually disappears;[4] but there is some epidemiological evidence in support of the view that animals occasionally carry contagion for some weeks after clinical recovery.[2,5] The virus is present in high dilution in the circulating blood early in the disease, before the vesicles appear. Furthermore, the typical lesions of the mouth and feet develop after infection by intravenous, intraperitoneal or intramuscular injections,[3] and occasionally follow the feeding of gelatin capsules containing lymph.[3] The disease must therefore be regarded as a general systemic infection, and the usual distribution of the lesions in the mouth and on the feet must be due as much to a special susceptibility of these tissues to the virus as to the fact that these locations constitute the usual portal of entry of the infection.

All attempts to demonstrate or to cultivate the microorganism causing the disease have been unsuccessful. However, Loeffler and Frosch[3] in 1898 showed that the lymph from a vesicle did not lose its virulence after it was diluted 1 to 40 in water and then passed through a Berkefeld filter. The disease therefore is one of those that are caused by a filterable virus, and the causative agent is probably ultramicroscopic.

The virus is relatively non-resistant.[3] It is quickly destroyed by light, heat, drying and disinfectants. It dies out within 12 hours if the lymph is kept at body temperature. It is killed by heating for 30 minutes at 70° C., and usually, though according to Loeffler not always, at 60° C. Thorough pasteurization should therefore render the milk non-infectious; but to insure absolute safety from infection, milk from diseased animals, if used at all, should be boiled. The virus is fairly resistant if kept cool and moist. In this condition it clings very tenaciously to contaminated objects, and thorough disinfection is necessary to rid an infected district of contagion. Possibly some of the infections which have been regarded as indirect may have been due to direct contact with healthy carriers.

In cattle[2] the disease usually develops in from two to seven days after exposure, with slight fever, frequent pulse and loss of appetite. The mucous membranes of the mouth, lips, and

[1] Mohler, J.: Foot-and-mouth disease. Farmers' Bull. No. 666, U. S. Dept. Agric., 1915.

[2] Hutyra, F., and Marek, J.: Special pathology and therapeutics of the diseases of the domestic animals, Am. Ed., I, 328. Mohler & Eichorn, Chicago, 1914.

[3] Loeffler and Frosch: Berichte der Komission zur Erforschung der Maul- und Klauenseuche bei dem Institut für Infektionskrankheiten in Berlin. Centralbl. f. Bacteriol., I Abt., 1898, XXIII, Orig., 371.

[4] Schütz: Impfversuche zum Schutze gegen die Maul- und Klauenseuche. Arch. f. Thierheilk., 1894, XX, 1.

[5] Loeffler: Die Schutzimpfung gegen die Maul- und Klauenseuche. Deutsche med. Wchnschr., 1905, XXXI, 1913.

often of the pharynx, become inflamed, deeply injected and very tender. The animals refuse all food. Salivation develops early, and because of the pain on swallowing, the saliva accumulates and drools from the mouth. The animals become listless and stand quietly unless forced to move. They rapidly become emaciated. The milk is greatly reduced in quantity and is often so changed in consistency and taste as to be unfit for use. After two or three days vesicles appear on the lips, gums, cheeks and upper jaw, attaining a diameter of 1 to 3 cm. The fluid is at first clear, but often becomes cloudy or purulent if secondary infection occurs. A little later vesicles usually appear on the feet, especially on the skin of the coronary band, on the heel and between the toes. When the feet are involved the animals become lame and may be unable to walk, or even to stand. Lesions frequently occur on the udder. The mucous membrane of the milk ducts may be involved, and even the parenchyma of the gland. In such cases the milk is highly infectious; it is not infectious if the udder is free from disease.[6] After one to three days the vesicles rupture, leaving superficial, deeply injected, very tender ulcers, which gradually heal unless secondary infection takes place. This frequently occurs in the ulcers on the feet, and if neglected often results in the formation of abscesses, which may burrow deeply and lead to loss of hoofs, serious damage to the joints, and even to death from pyæmia. Recovery, however, is the rule.

In adult animals the average mortality is only about one-half of one per cent.[7] In some epidemics, however, the disease appears in a malignant form, the mortality reaching 50%, or even a much higher figure. Death in such cases may be apoplectiform, due to a degeneration of the myocardium, or may result from a bronchopneumonia. In calves there is often a severe gastro-enteritis, and the mortality is high—about 20% or over.

Animals which survive the infection acquire some immunity, but only for a limited period. Recurrences are uncommon during the first year, but in some instances have occurred within six weeks.[7] It is possible to immunize animals artificially,[8] either actively by vaccination (result very uncertain) or passively by injections of immune serum; or by a combination of the two methods. But no method of any practical value has been devised, for the results are uncertain, the more effective procedures are dangerous, the immunity when obtained is of short duration, and all methods at hand are very expensive.

The occurrence of the disease in man has been recognized for more than two centuries. A large number of reported cases of human infection have been collected by Bussenius and Siegel.[9] Their report quite exhaustively covers the literature from 1695 to 1896. While some of the reported cases may be questioned, others are of undoubted authenticity and demonstrate the frequence of human infection. The apparent rarity of the disease in man is due in part to the facts that it usually runs a mild course and that it occurs most frequently in the poorer class of peasants, who rarely consult a physician for minor ailments. Most of the recorded cases have been observed by veterinarians and reported in foreign veterinary journals, which are seldom read by physicians and which are practically inaccessible in this country. The disease occurs in man in regions in which it is widespread among cattle. That it is not rare in such circumstances is shown by the fact that from 1887 to 1894 six hundred cases in man were officially reported in Germany.[10] It may be contracted by direct contact with diseased animals,[11] or by ingestion of infected milk or cream,[12 9] butter [13 14] or cheese.[15] The use of infected milk has given rise to extensive epidemics in which entire families, and even communities have been attacked.[16] Children are especially susceptible. The possibility of human infection following the use of contaminated milk was demonstrated experimentally by Hertwig in 1834.[12] Hertwig and two of his assistants each drank a quart of milk from a cow known to be infected. All three developed a typical attack of the disease. According to Demme [17] milk is infectious even when used in coffee. The sporadic cases occur most frequently in stablemen, butchers, milkers, and others who come into direct contact with diseased animals. The infection is probably transmitted through abrasions of the skin of the hands or of the mucous membrane of the nose and mouth.

The symptoms of the disease as described in man [18 19 20] are very similar to those observed in cattle. In the majority of cases it takes a mild form. After an incubation period of two to five, or even ten days, the disease usually sets in with fever of moderate severity, some general malaise and prostration, and a feeling of dryness and burning in the mouth. The

[6] Nocard: Rev. gén. de méd. vét., Toulouse, 1903, I, 369. Cited by Koránji (19). (Original reference not accessible.)

[7] Strebel. Cited by Caspar (8). (Original reference not accessible.)

[8] Caspar, M.: Immunität bei Maul- und Klauenseuche. Kolle and Wassermann's Handb. d. path. Mikroorg., Aufl. II, 1913, VI, 214.

[9] Bussenius and Siegel: Kann die Maul- und Klauenseuche des Viehes auf den Menschen übertragen werden? Ztschr. f. klin. Med., 1897, XXXII, 147.

[10] Amtliche Mittheilungen der Jahresberichte über die Verbreitung von Thierseuchen im deutschen Reiche. Collected and cited by Bussenius and Siegel.[9]

[11] Nowikow: Arch. f. vet. Med., 1893, II, 261. Cited by Bussenius and Siegel.[9] (Original reference not accessible.)

[12] Hertwig: Uebertragung thierischer Ansteckungsstoffe auf Mensch. Berl. med. Ztg., 1834, Nrn. 48-50, S. 225. Cited by Bussenius and Siegel.[9] (Original reference not accessible.)

[13] Fröhner: Ein Fall von Uebertragung der Aphthenseuche (Maul- und Klauenseuche) vom Rinde auf den Menschen durch Süssbutter. Ztschr. f. Fleisch- u. Milchhyg., 1891, I, 55.

[14] Lorenz: Uebertragung der Aphthenseuche auf den Menschen durch Genuss von Süssrahmbutter. *Ibid.*, 1893, III, 176.

[15] Schneider, J.: Neueste Erfahrungen über die Maul- und Klauenseuche des Rindviehs, des Schafe, Schweine, etc. Ann. d. Staatsarzn., 1840, V, 1.

[16] Siegel. Die Mundseuche des Menschen (stomatitis epidemica), deren Identität mit der Maul- und Klauenseuche der Hausthiere, etc. Deutsche med. Wchnschr., 1891, XVII, 1328.

[17] Demme, O.: Ueber die Uebertragung der Maul- und Klauenseuche durch die Milch. Wien. med. Bl., 1883, VI, 8.

[18] Glaister, J.: A case of foot-and-mouth disease in the human subject. Lancet, Lond., 1896, II, 872.

[19] Koránji, F.: Die Maul- und Klauenseuche. Nothnagel's Speziel. Path. u. Ther., 1897, V, 5 Th., I Abt., 137-150.

[20] Boggs, T. R.: Foot-and-mouth disease. Osler's Modern Med., Ed. 2, 1913, I, 1025.

FIG. 1.—Shows the appearance of the hand on the seventh day. Note the blotchy erythematous areas surrounding the flat papules, four of which are capped by unruptured vesicles; also in two areas, the shallow excoriations following rupture of the vesicles.

FIG. 2.—Shows the vesicles on the lips and tongue on the seventh day. Note the intense dusky red color of the mucous membrane.

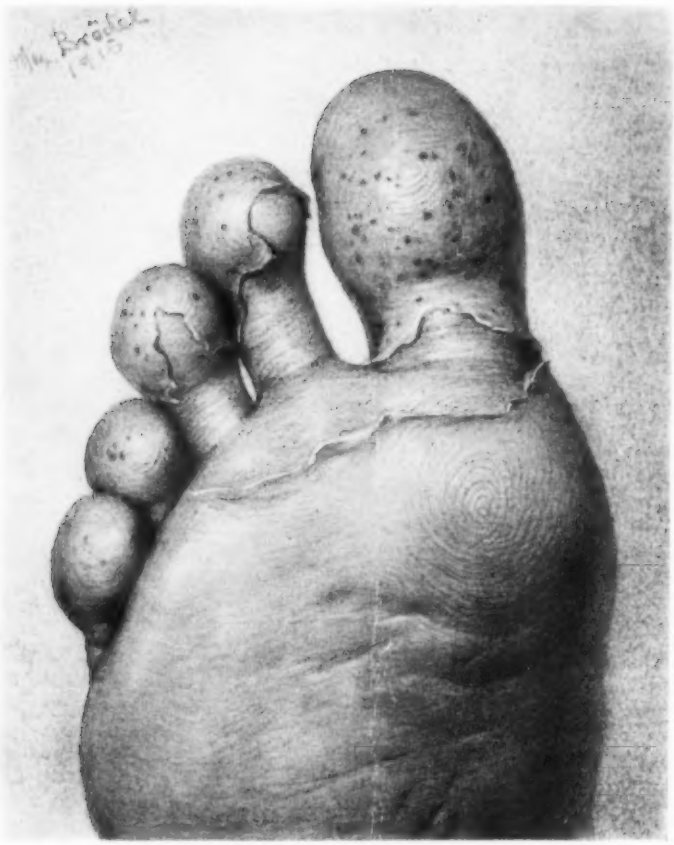

FIG. 3.—Shows the appearance of the foot on about the tenth day, after desquamation had begun. Note the small reddish-brown areas of fading purpura over the toes where desquamation had not yet occurred.

mucous membrane of the lips, cheeks and gums becomes deeply injected and sore. Salivation develops. After two or three days small vesicles appear at these locations, and also on the edges and ventral surface of the tongue, and in the pharynx; more rarely also on the hard palate, in the nose, on the conjunctiva, or on the skin adjacent to these regions. With the appearance of the exanthem the fever and the constitutional disturbances usually subside. The vesicles attain a diameter of 2 to 10 mm., though adjacent ones may coalesce to form larger blebs. They contain a clear or slightly cloudy fluid, which may subsequently become purulent. There is usually swelling of the tongue and lips, sometimes of the nose, and even of the entire face. After two or three days the vesicles rupture, leaving superficial, deeply injected, very tender ulcers, which heal quickly and without scarring unless secondary infection occurs. There is moderate swelling of the regional lymph glands, and often of the salivary glands. Until healing takes place the burning, pain and tenderness in the mouth are intense. There is profuse salivation and great pain on eating, speaking or swallowing.

In the mild forms, which constitute the great majority of all human cases, there may be no symptoms other than the appearance of a few vesicles in the mouth. In the more severe cases, usually shortly after the appearance of the vesicles in the mouth, similar vesicles appear on the skin of the hands and feet. The hands are most often affected, and the eruption is rarely limited to them. The lesions are most numerous on the finger-tips, on the volar side of the fingers and at the base of the nails. Less often they occur at the base of the fingers, on the middle of the hand or the arms. Swelling, itching and burning of the fingers and toes often precede the appearance of the eruption. If the feet are involved, the vesicles usually occur on the toes and heel. They occasionally occur on the genitals and about the nipples. Very rarely they may be disseminated over the whole body. They rupture and heal much as do those in the mouth. Secondary infection of the ulcers on the toes or fingers may lead to loss of the nails. In severe cases petechiæ have been described.[20 21]

In children, and less often in adults, there may be more serious general symptoms, with chills, high fever, colicky abdominal pain, nausea, vomiting, and diarrhœa with bloody stools. Such cases may end fatally, as may those in which serious secondary infections occur. During a severe epidemic near Berlin, reported by Siegel,[19] out of a population of 9,000 it was estimated that two-thirds contracted the disease during a period of three years. There were 36 deaths attributed to the infection, 15 in children and 21 in adults.

Proof of the identity of the disease in man and animals has been furnished by Schautyr[22] and by Bertarelli,[23] who each transmitted the disease to calves by inoculation with a virus obtained from a human subject.

The case here reported corresponds closely in its essential features to the published descriptions of the disease:

C. L., white, male, medical student, aged 20. Admitted December 26, 1914.

Complaint. Sore throat.

Family History. Unimportant.

Past History. General health excellent. Measles, mumps and scarlet fever in childhood. Received a prophylactic dose of diphtheria antitoxin after scarlet fever. No other acute illnesses. No venereal infection. Habitual smoker.

Patient's home was in Nebraska, but from October 1, 1914, he had been in regular attendance at the Johns Hopkins Medical School, and had not been in the country, or out of the city, until December 24, one day before the onset of the present illness, when he had gone to Washington, D. C. He had not been in contact with any animals. He had drunk no milk, but had eaten butter and had used cream with coffee, etc. No case of a similar nature was known in his boarding house or in the neighborhood.

Present Illness. Onset December 25, the day before admission, with burning and soreness of the feet. The following morning he noticed a dry taste in his mouth, "like alum"; this rapidly increased to a painful, burning sensation, and the throat became very sore. The pain in the toes increased, and they became tender, red, swollen and numb. There were no other symptoms, and no general discomfort.

Physical Examination. On admission, the night of December 26. Robust, well-nourished, healthy-looking man. Temperature 99.8°; pulse 100; respirations 20. No especial discomfort. Face very slightly swollen. No eruption on skin. Glands palpable at the angle of the jaws. The chest and abdomen showed nothing of importance. The spleen was not felt, though it became palpable on the tenth day.

The tongue was moist and coated. The mucous membrane of the mouth was rather dry and red. The tonsils were only slightly enlarged. The pharynx and tonsils were deeply injected, as were also the posterior portion of the soft palate, and the cheeks, especially along the line of closure of the teeth, where there were several small, slightly elevated, yellowish areas of exudate, 1 to 3 mm. in diameter. The posterior pharyngeal wall and the tonsils were covered with a thin layer of greyish muco-purulent exudate, which was very readily removed with a swab. There were no ulcerations.

The toes and feet were swollen as far back as the metatarsophalangeal joints. The skin was tense, deep red and tender. Tingling and intense itching were complained of.

Smears from the throat showed no fusiform bacilli or spirilla. There were a few bacilli suggestively beaded at the ends. Diphtheria antitoxin (5000 units) was accordingly given, but cultures later proved to be negative for diphtheria.

By the third day (December 27) the inflammatory process in the mouth had extended very markedly. The inner surfaces of the cheeks and lips were involved; also the ventral surface and lateral margins of the tongue, and the grooves between the tongue and the gums and between the gums and the cheeks. The mucous membrane was intensely red, raw and very sore. There were numerous small, slightly elevated, yellowish areas, 2 to 5 mm. in diameter, which in places coalesced to form areas 1 to 2 cm. in diameter. Marked salivation developed. By the fourth day the process had extended until practically all the visible mucous membrane had become involved, including the hard palate and

[21] Boas: Maul- und Klauenseuche beim Menschen. Deutsche med. Wchnschr., 1893, XIX, 972.

[22] Schautyr: Beiträge zur Lehre der Maul- und Klauenseuche beim Menschen. Arch. f. vet. Med., 1893, II, 87. Cited by Koránji.[19] (Original reference not accessible.)

[23] Bertarelli: Uebertragung der Maul- und Klauenseuche auf den Menschen und Wiederimpfung der menschlichen Krankheit auf die Rinder. Centralbl. f. Bakteriol., I. Abt., 1907, XLV, Orig., 628.

dorsal surface of the tongue. Here there were numerous small nodular elevations, about 2 mm. in diameter, some translucent but most of them yellowish and opaque. On close inspection it was evident that they were minute vesicles or pustules. On inserting the point of a platinum needle under the margin of one of these yellowish areas it could be made out that the exudate was in reality epithelium, raised slightly above the level of adjacent. more normal mucous membrane, and free, except at the margins, from the underlying tissue. When the exudate was removed, a raw, angry-looking surface was exposed. The lips were involved as far as the muco-cutaneous junction. They were cracked and very red, and showed several large, flat pustules. At no time was there any eruption on the skin of the face.

On the fourth day an eruption appeared on the palms and backs of the hands. It consisted of small papules, 3 to 5 mm. in diameter, surrounded by a wider area of erythema. Later some of these papules developed into vesicles and pustules. A few papules appeared over the carpus, but none on the arms or trunk. There was marked itching, burning and tingling of the hands and especially of the feet. The feet became swollen, the skin tense and deeply red. No papules appeared on them. The skin on the plantar surface of the toes and balls of the feet became mottled with small translucent spots, like minute sago grains, due to small accumulations of fluid beneath the epithelium. In a few places on the toes these later coalesced to form flat vesicles, 0.5 to 1 cm. in diameter. Very numerous, minute, pin-point hæmorrhages appeared in the skin of the plantar surface of the toes, and a day or two later over the sole and heel. These were most numerous on the great toes. As the color faded the skin had the appearance of being sprinkled with nutmeg. Later the skin cracked in the grooves on the flexor surface of the toes and oozed freely. The eruption gradually subsided after the seventh day, and was followed by complete desquamation over the hands and feet. The appearance of the lesions on the seventh day is well shown in the accompanying illustrations.

By the tenth day the soreness and inflammation in the mouth had begun to subside. The larger ulcers did not completely heal until the end of the third week. There was no scarring. The patient was discharged on the thirty-second day. There were still reddish blotches on the hands and some desquamation on the palms.

Except for 48 hours following the injection of antitoxin the temperature never rose above 100°. The Wassermann reaction was negative. The urine was normal. Hæmoglobin, 95 per cent. White blood cells 10,000. Differential count (sixth day):

	Per cent.
Polymorphonuclear neutrophiles	73
Polymorphonuclear eosinophiles	1
Polymorphonuclear basophiles	1
Small mononuclears	12
Large mononuclears	9
Transitionals	3
Unclassified	1

Treatment consisted of mouth washes of potassium chlorate and permanganate, and the application of skin lotions to relieve the itching.

On the seventh day some of the exudate scraped from the vesicles in the mouth was inoculated into the mouth of a young dog after scarification of the mucous membrane. No lesion developed. There would have been a greater prospect of success had the inoculation been made at the first appearance of the vesicles—when they are most infectious—but the nature of the disease had not then been recognized. Unfortunately an animal more susceptible than the dog was not obtainable at the time.

The clinical picture presented was therefore that of a mild febrile infectious disease, characterized by the appearance of an erythema and a superficial vesicular eruption over the mucous membrane of the mouth and on the skin of the hands and feet; by salivation; by swelling, burning and parasthesias of the affected parts, with subsequent desquamation; and by healing of the ulcers without scar formation. This picture corresponds to that of foot-and-mouth disease and to no other recognized condition known to the writer. The disease was present at the time in cattle in the neighborhood of Baltimore, and infection by means of milk or cream was possible, though it could not be demonstrated. Experimental proof of the nature of the disease by animal inoculation could not be obtained. Nevertheless the clinical picture was so characteristic that the diagnosis seems reasonably certain.

In conclusion, I wish to express my indebtedness to Mr. Max Brödel for the preparation of the accompanying illustrations.

A METHOD FOR THE STUDY OF MORPHOLOGY AND REPRODUCTION IN FILAMENTOUS ORGANISMS.[1]

By Thomas R. Boggs, M. D., and M. C. Pincoffs, M. D.

(*From the Medical Clinic of the City Hospitals at Bay View, Baltimore.*)

The importance now accorded to fungi in human pathology, introduces a new and complex group of organisms to the medical investigator. The methods of study are difficult and confusing, and it has occurred to the authors that the technique they have used in such cases may be of interest to others.

Essentially, the method consists of the study in section of stab cultures in solid media. While it was independently developed, the principle is not new. We have recently found that some studies in this line were reported by Fischl in 1887, and since then a number of observers have published, in technical journals, modifications of these methods. For the most part, these are elaborate and slow. Fixation in Flemming's solution or in chromic and osmic acid mixtures, staining *en bloc*, paraffin embedding, etc., result in considerable shrinkage and consequent distortion. They have attracted little attention and are seldom used, even by experienced mycologists.

Briefly, our method is to transfer the organisms in question to stab cultures in heavy gelatin, of from 12% to 15%, specially prepared so as to be very clear, the tubes, which are not more than 12 mm. in diameter, being filled to a considerable depth. Many of these organisms grow luxuriantly in such media at room temperature, with production of filaments

[1] Read at a meeting of The Association for the Advancement of Clinical Investigation, Washington, D. C., May 10, 1915.

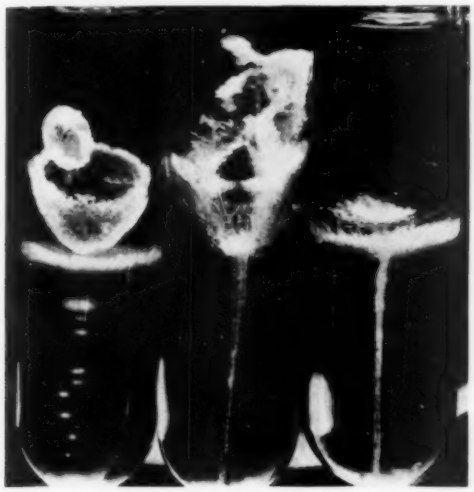

FIG. 1.

A "Yeast" Monilia(?)—From banana.
B "Yeast" Monilia(?)—Author's case.
C "Yeast" Monilia(?)—Ashford.

Thirty-day gelatin cultures magnified 2¼ diameters by reflected light. Gross morphology in old cultures is constant for some species.

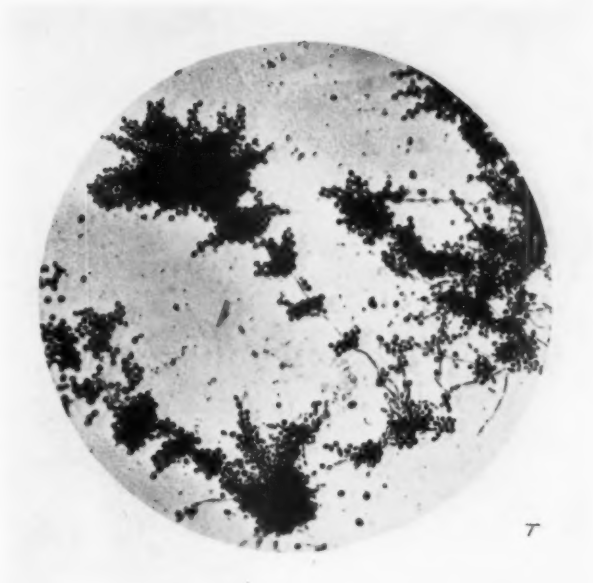

FIG. 4.—Endomyces albicans(?). From child with thrush. Fuchsin stain. (× 500 diam.)

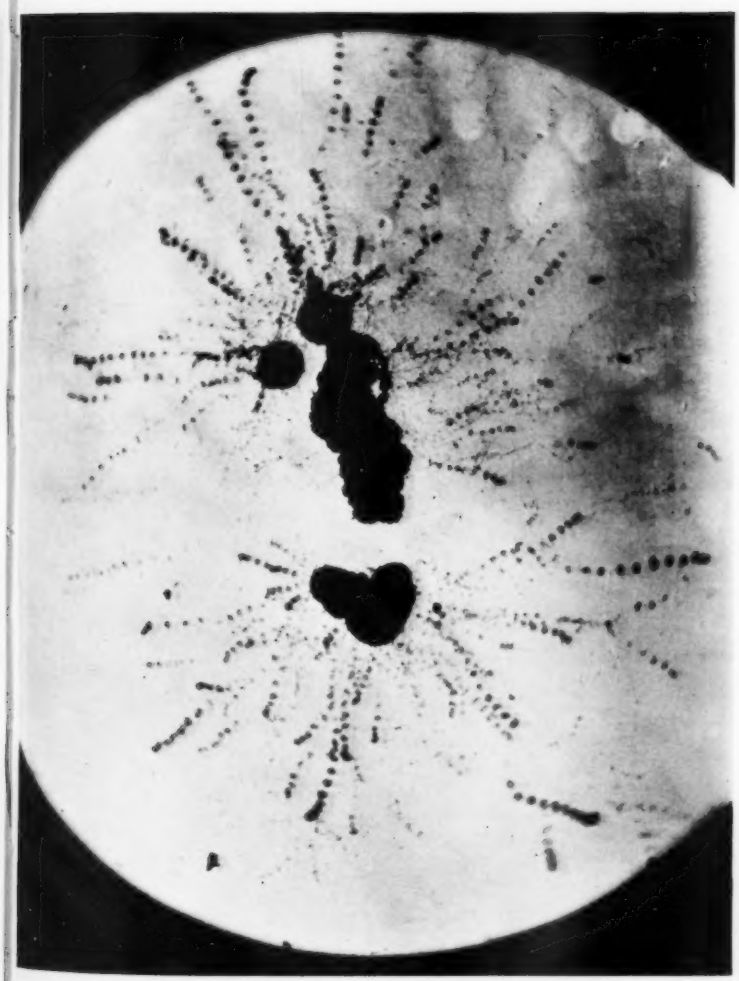

FIG. 2.—Monilia(?). Author's case. Section × 80 diam. Fifteen-day gelatin stab, Victoria Blue stain. Radial growth of threads and axial spore-clumps. Dark masses in center composed of spores similar in all respects to the axial spores on threads.

FIG. 3.—Monilia. Author's case. Section from 8-day gelatin stab, fuchsin stain. Fruiting hyphæ with lateral and terminal sporulation. (× 1000 diam.)

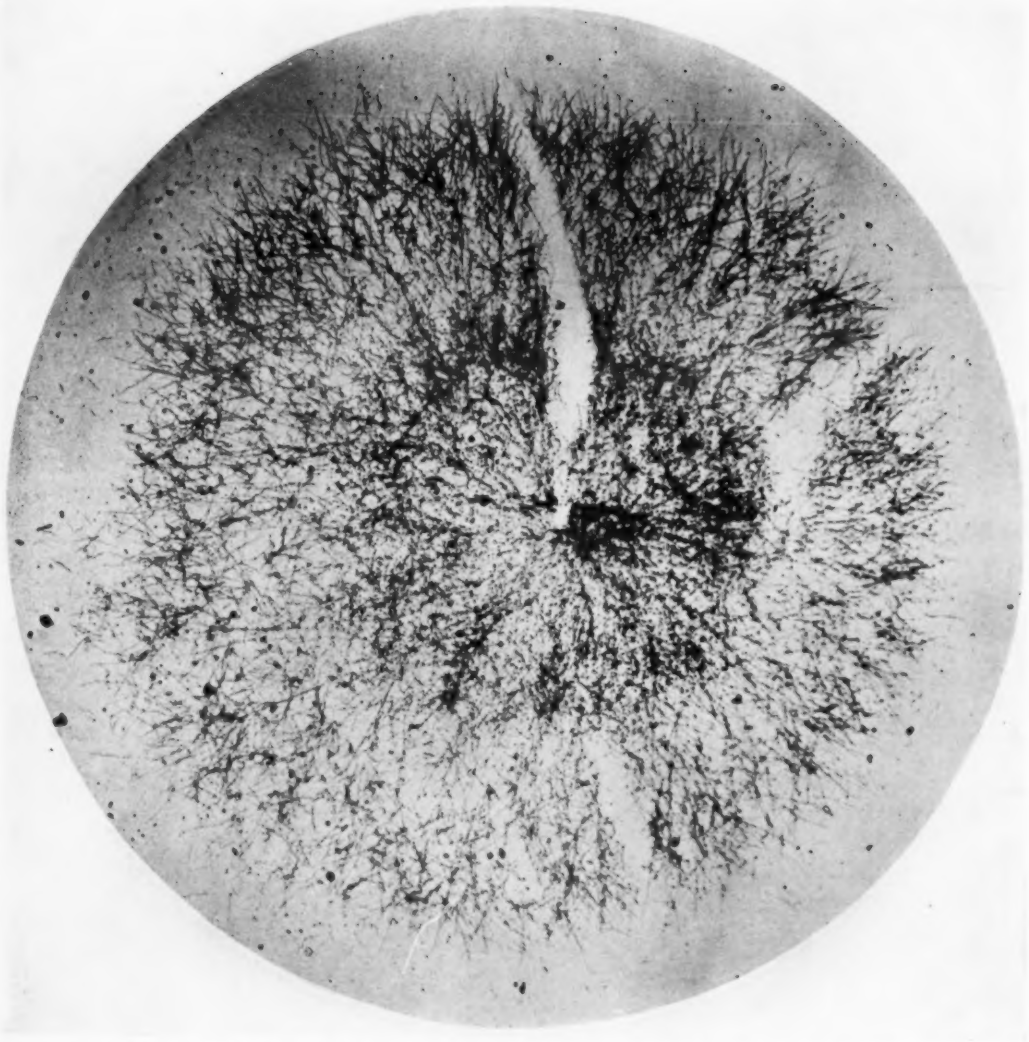

FIG. 5.—Trichophyton violaceum, 8-day gelatin. Crystal-violet stain. (× 300 diam.)

FIG. 6.—Monilia(?). Author's case. Section from 8-day gelatin stab, fuchsin stain. (× 1000 diam.) Hypha (A) with ordinary spores (B) and chlamydo spores (C) on same thread.

lateralward from the stab. When the development has reached the desired point, 10% formalin is poured on the top of the culture and the gelatin is hardened *in situ*. After 48 hours, the tube may be cracked and the glass peeled away from the gelatin, which is of a firm, somewhat rubbery consistency. Selected blocks are then cut from this culture and sections made with the freezing microtome. Where sections of the surface growth are desired, the culture is hardened as above, and the supernatant formalin is poured off and replaced by melted gelatin. After cooling, this top layer is also treated with formalin and, when hardened, blocks may be cut, including the surface growth in the direction desired. The thickness of the sections should be varied with the dimensions of the filaments and reproductive organs under consideration. Our sections have been from 10 to 25 microns.

These sections give an admirable picture of the relation of the filaments to the stab and of the various methods of sporulation developed in the culture. The threads, spores and other reproductive structures are held absolutely fixed in the relations in which they have developed. The sections may be studied unstained, including dark field illumination, or they may be stained in various ways. The aqueous methods of staining and of differentiation have seemed to us to be the most rapid and to produce the least distortion. We have employed for this purpose dilute carbol-fuchsin, one to thirty (of the standard stain for tubercle bacilli), staining from 12 to 24 hours. The heavily stained sections are then differentiated rapidly in a saturated citric acid solution. When the desired decolorization is reached, the sections are washed in water, mounted on a clean slide, drained and allowed to dry in the air without blotting. When thoroughly dry they are rapidly cleared in xylol and mounted in balsam. In order to retain the stain in the filaments the decolorization must be stopped while the medium is still distinctly pink. This stain is of especial value for the details of cell structure under high powers. For the study of the general morphology and the spatial relations of the filaments and reproductive organs, a stain which allows of more complete decolorization of the medium is desirable. The sharper contrast thus obtained results in a schematic picture of the growth. For this purpose Victoria Blue (at the suggestion of Maj. B. K. Ashford) is used (one part of a saturated alcoholic solution to 50 parts of distilled water). The sections are stained overnight, mordanted for one to two minutes in Lugol's solution, washed in water, and decolorized in 95% alcohol. The decolorization should be frequently interrupted by transferring into distilled water, where the depth of color retained may be observed. When the medium shows only a faint blue tinge, in contrast to the deeply stained organism, the sections are floated on slides and air-dried. Then after clearing in xylol they are mounted in balsam. Such sections show the organisms stained deeply blue to bluish-black; the filaments and cells being specially sharp, while the internal structure is not so well differentiated. These preparations are particularly adapted to photographic reproduction.

The crucial advantage of these methods is the fact that the spatial relations of the different parts of the organisms are exactly preserved; a point which cannot be overestimated as an aid in the classification of the organisms. The gelatin cultures also lend themselves admirably to the study of the gross morphology of filament production, as is illustrated in the accompanying photographs.

Furthermore, we have found that organisms which do not grow at room temperatures (such as are alone suitable for gelatin cultures) may be studied in a similar manner by using a medium composed of 1% agar-agar and 7% gelatin, carefully cleared as in preparing the gelatin medium. This will stand up in the thermostat and in our hands has given excellent sections, which stain quite as well as the gelatin, but which require more care in handling as they are more friable.

The medical and technical books on mycology, for the most part, make no mention of such methods of study, and it is our impression that the neglect of these methods adds to the difficulty in recognizing the type forms of these organisms. Morphological details are at present the main dependence in classification, and the only hope of satisfactory identification of a given organism may lie in the persistent use of rich culture media and the study of the organism morphologically, at various stages of its development. Organisms which in the early period after isolation present only a small yeast-like form, after repeated transfers and changes of media may develop one or more characteristic methods of reproduction; and until these are found and properly identified the classification of the organisms is incomplete. The wide variation in cultural characteristics, especially in the reactions produced in carbohydrate media, makes identification by such methods difficult and confusing. The same strain of an organism in culture often exhibits marked changes in its reaction toward specific carbohydrates.

It is to be hoped that this morphological method may be more widely employed and lead to a better and clearer classification of these very confusing groups.

The best of our micro-photographs we owe to the unfailing kindness of Prof. Erwin F. Smith, of Washington, D. C.

We wish especially to express our thanks to Doctors M. C. Winternitz and W. W. Ford, for their assistance in furnishing laboratory facilities.

JOHNS HOPKINS HOSPITAL BULLETIN.

The Hospital Bulletin contains details of hospital and dispensary practice; abstracts of papers read and other proceedings of the Medical Society of the Hospital, reports of lectures, and other matters of general interest in connection with the work of the Hospital. It is issued monthly. Volume XXVI is now in progress. The subscription price is $2.00 per year. (Foreign postage, 50 cents.) Price of cloth-bound volumes, $2.50 each.

A complete index to Vols. I-XVI of the Bulletin has been issued. Price 50 cents, bound in cloth.

A STUDY OF THE FERMENTS AND ANTIFERMENTS OF THE BODY AND THEIR RELATION TO CERTAIN DISEASES.*

By Jas. W. Jobling, M. D., and William F. Petersen, M. D.

(From the Department of Pathology, Vanderbilt University Medical School, Nashville, Tenn.)

During the past few years much work has been done to prove that immunity from infection is due to the presence of specific ferments. Vaughan[1] was able to obtain toxic substances by hydrolyzing proteins with alcoholic potash; he therefore concluded that intoxications accompanying infections are due to the production of poisons liberated through the action of specific proteolytic ferments. More recently Abderhalden,[2] by means of the polariscope and of dialyzing membranes, has elaborated a technic whereby he claims that he can demonstrate the presence of specific ferments in the blood of pregnant women which are capable of splitting the placental protein. The work of these two authors and the views which they advance render it necessary to determine if the body can generate ferments which will attack only certain native proteins.

In order to determine if the ferments of the body are capable of producing toxic substances from native proteins, one of us (Jobling) with Strouse[3] studied the cleavage products obtained by the action of leucoproteose on various proteins. Opie,[4] Müller[5] and others, had already shown that leucocytes contain very active ferments. We found that these cleavage products are toxic and that the toxicity is almost wholly confined to the primary proteose fraction.

Similar results were obtained by treating bacterial proteins with leucoproteose. It was found that the toxic substance is bound up with the native protein and cannot be separated from it excepting through the action of ferments. All those means by which the native bacterial protein is removed from a freshly prepared solution, leave a comparatively non-toxic filtrate, though boiling a solution made slightly alkaline to prevent coagulation does not destroy the toxicity. On the other hand, toxic substances free from native protein may be obtained through the action of leucoproteose, and they are also present in the primary proteose fraction. These results do not necessarily mean that there are no true secretory toxins, but show that toxic substances may be produced by hydration of the bacterial proteins.

Antiferments.

With the knowledge that toxic substances may be derived from proteins as a result of the action of proteolytic ferments normally present in the body, we deemed it necessary to make a more careful study of the substances which inhibit the action of proteases.[6]

In our first experiments we studied the ferment-inhibiting agents contained in tubercle bacilli and in tuberculous caseous material. We studied caseous material because of the fact that its production in tuberculosis must be partly due to the presence of substances which inhibit the action of the ferments set free as a result of the disintegration of the cells.

In these experiments we found that suspensions of the ether and alcoholic extracts of tubercle bacilli were inactive as antiferments, but that the soaps prepared by saponifying the extracts with sodium alcoholate were very active. The inactivity of the unsaponified extracts in sodium chloride solution is probably due to the coarseness of the suspension.

Having found that soaps prepared in this manner were actively antitryptic, we then tested them to see if their activity was due to their degree of unsaturation. The fatty acids were treated by the ether-lead soap method, and the ether soluble fraction was tested for its ferment-inhibiting action. This method, of course, does not give a complete separation of the saturated and unsaturated fatty acids, but the separation was sufficient to prove to us that the unsaturated fatty acids are the active agents. It was further found that saturation of the unsaturated carbon bonds with iodin, or with hydrogen peroxide, would destroy their antiferment activity.

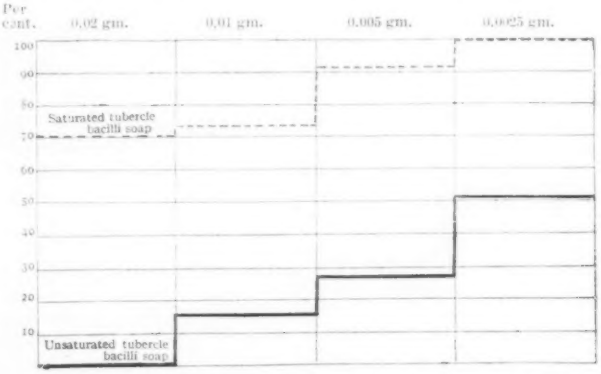

Chart 1.—Effect of saturated and unsaturated soaps of tubercle bacilli on tryptic digestion.

Similar results were obtained with the caseous material from tuberculous lymph-glands and from caseous pneumonia. The ferment-inhibiting substances, the esters of the unsaturated fatty acids, were found in all material examined, but in relatively small amounts when the caseous material had been secondarily infected. This is probably due to the dilution and washing out of the esters.

These results shed considerable light on the action of iodides in tuberculosis. Tubercles and caseous areas may be present in the lung, but unless they open into the air passages tubercle bacilli may be absent in the sputum. If iodides are now given the caseous matter begins to soften, and is more likely to rupture into the bronchi, and the bacilli are then discharged in the sputum.

*Read before The Johns Hopkins Hospital Medical Society, February 15, 1915.

The sudden discharge of the softened caseous material into the bronchi as a result of the action of the iodin, would also explain the occurrence of hemorrhages, as it would leave unsupported any blood-vessels traversing the mass whose walls had been involved in the tuberculous process to a degree that would render them unable to withstand the blood pressure without some outside support. We must also bear in mind the possibility that with the softening and absorption of these caseous areas, the tubercle bacilli may be disseminated.

Ferment-Inhibiting Action of Soaps.

Having shown that soaps of the unsaturated fatty acids obtained from tubercle bacilli and tuberculous caseous material inhibit the action of trypsin and leucoproteose, we thought it necessary to determine if other unsaturated fatty acids possessed the same property. In order to obtain some information on this point we prepared soaps from oils known to contain a large number of unsaturated fatty acids. For this purpose we used linseed oil, hempseed oil, castor oil, olive oil, croton oil and cod-liver oil, and found that the activity of these soaps as ferment-inhibiting agents is dependent upon the degree of the unsaturation of the fatty acids, and is in proportion to their iodin value. The most active soaps were obtained from tubercle bacilli.

Serum Antitrypsin.

Having obtained some definite information concerning the nature of the ferment-inhibiting substances present in tubercle

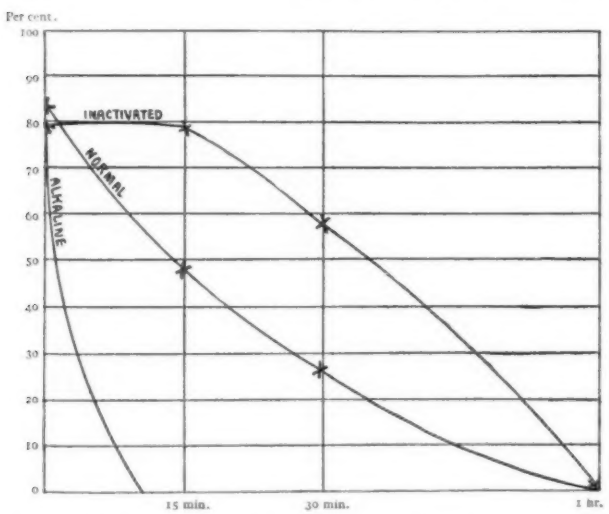

Chart 2.—Rate of removal of serum antitrypsin in normal, inactivated, and alkalinized serum at 37° C., when treated with chloroform.

bacilli and in tuberculous caseous material, we next turned our attention to the so-called antitrypsin of the blood.[7] We wished to see if this action of sera was due to the same agent.

Considerable work has been done by Schwartz,[8] Sugimoto,[9] Meyer[10] and Kirchheim[11] with lipoid solvents in order to show the relation between the lipoids of the serum and antitrypsin, but with contradictory results. The experiments were made with fresh serum from dogs, human beings, guinea-pigs and rabbits. We found that the antitryptic action became almost wholly lost in sera extracted several days at room temperature with chloroform or ether, and was wholly lost when they were incubated with chloroform at 37° C., for 60 minutes.

These experiments have been repeated and similar results have been obtained each time. It is necessary to shake the mixtures of chloroform and ether frequently, and at least twice as much solvent as serum should be used, otherwise the inhibiting action of the serum is not removed.

The chloroform and ether does not destroy the antitrypsin, as it can be recovered from the solvents almost quantitatively by appropriate means. A large portion of the antiferment action may be destroyed by incubating the serum over night with iodin and potassium iodide. This is due to the saturation of the unsaturated carbon bonds.

It is well known that the antitryptic action of the serum is destroyed if heated for 30 minutes at 70° C. This also occurs when the mixtures of the unsaturated soaps with protein substances are treated in the same manner. It is difficult to explain why this occurs. Thinking that it might be due to the coagulation of the proteins, we made protein-soap mixtures strongly alkaline with sodium hydrate and heated them to 70° C., for 30 minutes. They were then neutralized, and tested, and found to be still active as antiferments. As yet we have been unable to find any satisfactory explanation of this phenomenon. The iodin values of the heated and unheated mixtures are the same, so we must assume that the combination formed is one which is readily dissociated.

Serotoxins.

In view of the fact that many sera contain proteolytic ferments, we made experiments to determine whether such sera would become toxic for animals of the same species if the antiferments were removed.[12] The experiments were based on the idea that the ferments would act upon the exposed serum proteins.

In order to remove the antiferment, guinea-pig serum was incubated over night with two volumes of chloroform. It was then centrifuged and the clear serum filtered through coarse filter paper until the chloroform in solution had evaporated. It was found that serum of guinea-pigs treated in this manner was toxic for other guinea-pigs in doses of 0.003 cc. to 0.01 cc. per gram weight. The symptoms and post-mortem findings were similar to those observed in anaphylaxis. Subsequent experiments conducted with oxidizing agents such as free iodin gave similar results.

When the chloroform-serum mixture is incubated at 37° C., the serum becomes most toxic after 24 hours, and begins to lose its toxicity at the end of 48 hours. In some experiments, though, we observed that the toxicity reached its maximum within from 8 to 12 hours. This depends entirely upon the rate of removal of the protective lipoid substances. The increase in the toxicity of the serum runs almost parallel with the increase of non-coagulable nitrogen.

We have already shown that the toxic fraction of the protein cleavage products lies in the primary proteose fraction, and that the continual action of the ferment soon renders it non-toxic owing to the further cleavage. The decrease in toxicity noted in the above experiments is probably due to the same cause. Freshly prepared serotoxins show no increase in non-coagulable nitrogen, and toxic split-products cannot be isolated by fractionating the serum with ammonium sulphate. These results indicate that exposed serum-proteins are split to toxic substances when injected into the circulation of animals. We have termed the poison developed in this manner, "serotoxin."

We observed during the course of the work that when excessive doses of the serotoxins were given the post-mortem revealed extensive intra-vascular coagulation of the blood. On the other hand, minimal doses appeared to lengthen the

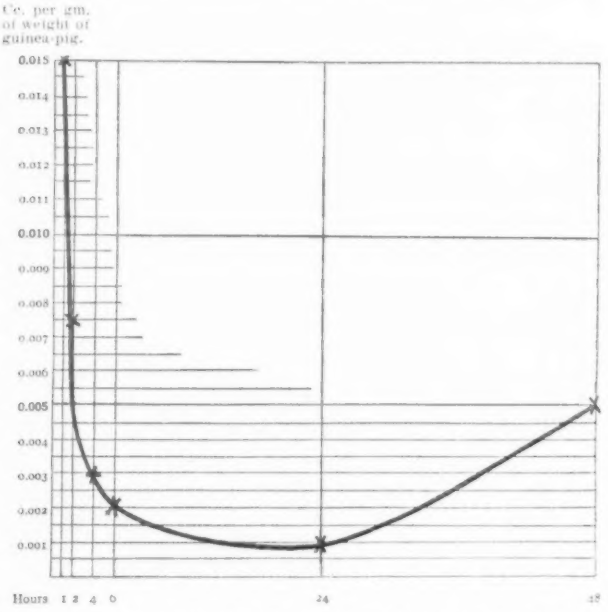

CHART 3.—Curve showing the increase of toxicity of guinea-pig serum treated with chloroform at 37° C. Minimum lethal dose in cc. per gm. of weight.

coagulation time. This caused us to consider the possibility of emboli being the cause of death, even when small doses were given. In order to rule out this factor, we gave a series of guinea-pigs large amounts of hirudin intravenously five minutes before injecting the toxin, and then gave large and small amounts of the toxic sera. There were no evidences of intravascular coagulation in the animals that died as a result of the action of the toxin. We shall not attempt to explain why intravascular coagulation should follow the intravenous injection of these substances, but wish to state that similar results are obtained following the intravenous injection of the soaps of the saturated and the unsaturated fatty acids.

If we are correct in assuming that the toxicity of the serum is due to the removal of the protective substances, then by returning these extracted substances the serum should become non-toxic. It is practically impossible to restore the lipoids to the serum in the fine state of dispersion in which they are active, and so they were saponified and used in the form of soaps. By the use of this method it was found that we could neutralize the toxicity of freshly prepared serotoxin. If, on the other hand, we used the serotoxin prepared by extracting the serum for 24 hours at 37° C., the toxin could not be neutralized. This indicates that the soap is of value only in so far as it prevents the formation of the toxin, and that it cannot neutralize those which are present at the time the soap is added.

Freshly prepared sera are much more toxic for animals in which the normal antitrypsin has been reduced by painting the shaved skin with tincture of iodin. The antitrypsin of the serum of guinea pigs treated in this manner is greatly decreased, and they succumb when given one-third to one-fifth the amount of serum necessary to kill a normal animal.

ANAPHYLATOXIN.

The similarity of the results obtained by us with serotoxin and those obtained by Friedberger,[13] Doerr,[14] and others with the so-called anaphylatoxins, suggested to us the possibility that the toxins obtained by treating bacteria with fresh guinea-pig serum might also be derived from the serum instead of from the bacteria, as is generally supposed. This view is confirmed by the work of Friedemann,[15] Ströbel,[16] Bordet,[17] and other investigators, who have obtained preparations toxic for guinea-pigs by treating fresh guinea-pig serum with kaolin, agar, Kieselguhr, starch, waxes and fats from bacilli, besides the true antigens, which last need not be specific, for they are still effective after boiling. It has also been shown that the complement is not essential, for toxic sera can be produced from inactivated serum, although not with the same regularity as from active serum.

Briefly, we found that those agents, which are most effective in making the guinea-pig serum toxic, are also most effective in removing the antitrypsin; in almost every instance the toxicity bore a definite relation to the degree of the removal of the antiferments.[18]

Most authors working on this subject believe the toxicity of anaphylatoxins to be due to the toxins derived from the bacterial bodies; hence a large portion of our work was done with bacteria. We wished to determine, first, if bacteria adsorbed such antiferments and thus exposed the serum proteins to the action of ferments and, secondly, if there was a loss of bacterial nitrogen as a result of the treatment. As a result of these experiments we found that the bacteria adsorb the antiferments as readily as kaolin, agar, starch, etc., and that they become much more resistant to the action of trypsin.

In most of these experiments in which known quantities of bacteria, as determined by the total nitrogen present in the emulsion, were used, we found that the bacteria treated with serum were not destroyed. In fact the total nitrogen in the bacteria thrown down in the centrifuge, and then washed thoroughly, was as high if not higher than in those treated with salt solution.

Dold [19] observed that anaphylatoxins could not be obtained with bacteria which had been treated with oils or with cholesterol. We confirmed the work of Dold, and believe that the results are due to the saturation of the bacteria with the oils or cholesterol to such a degree that they are unable to take up the lipoids of the serum. In confirmation of this view we observed that serum mixed with bacteria which had been treated in this manner does not lose its antiferment as it does when mixed with untreated bacteria. Further, we found here, as in the preparation of serotoxin, that the toxicity of the product bears a definite relation to the degree of adsorption of the antiferment. These results would seem then to prove definitely that the toxicity of the anaphylatoxins is due to the presence of cleavage products derived from the proteins of the serum, and not from the bacteria.

Lipoids and Serum Antitrypsin in Anaphylaxis.

Rusznjak,[20] Pfeiffer and Jarisch [21] observed that the serum antitrypsin is increased following the recovery from anaphylactic shock; and we observed that the same thing occurred after a sublethal dose of serotoxin. We also found that animals recovering after having received an intravenous injection of serotoxin are able to withstand two or three times the minimum toxic dose if given within 24 hours. These results led us to consider the possibility of the refractory period following anaphylactic shock being due partially to this factor.[22]

We made a series of experiments on animals in which the antitrypsin had been increased to see if they could be made more resistant to a second dose of the specific protein used to sensitize them. The antitryptic strength was increased by giving the animals subcutaneous injections of serum lipoids dissolved in olive oil, and of fats prepared from egg-yolk. The guinea-pigs were sensitized with horse serum. The results of the experiments show that animals, whose antitryptic strength has been raised by injection of these lipoidal substances 24 hours previous to receiving the second and intoxicating dose, can withstand at least twice the minimum lethal dose of the antigen.

The knowledge that lipoids within certain limits may inhibit anaphylactic shock, caused us to study the toxicity of lipoid-free serum albumin, as a specific antigen in anaphylaxis. We found that the lipoid-free albumin used for the second and intoxicating dose was about four times as toxic as the unextracted albumin.

We have already mentioned that the lipoids of the serum when saponified will neutralize the toxicity of freshly prepared serotoxin, and this was also observed to be true of the second and intoxicating dose of serum albumin in anaphylaxis. It was found that sodium oleate can neutralize from five to six times the amount of serum albumin required to produce anaphylactic shock, but does not protect against the straight serum. Care must be taken in the use of sodium oleate, as in larger amounts it also will cause death with most of the phenomena observed in anaphylaxis.

Bacterial Antiferment.[23]

The resistance of bacteria to enzyme action, because of its importance as a factor in the defense of the invading organism against the destructive agencies of the host, has interested several observers, among them, Kruse,[24] Fermi,[25] Kantorwicz [26] and Weinkoff.[27]

The older conception that bacteria resisted digestion because of some vital property had to be discarded when it was found that organisms killed by chloroform, toluol, carbolic acid, etc., seemed to resist digestion as well as viable bacteria. It has so far been the implied idea that since bacteria contain protein, such protein should be an available substrate for enzyme action, in other words, that the bacterial cell represented a freely exposed mass of protein. In dealing with an intact cell there are, however, certain factors which indicate that this position is untenable.

Bacteria contain fats and lipoids in varying amounts, which, because of their marked effect on surface tension, would for purely physical reasons tend to become concentrated at the periphery of the colloidal system such as the bacterial protoplasm. Czapek [28] states that if the limiting membrane is similar to that present in plant cells it would consist chiefly of lipoidal substances.

With or without a morphologically distinct limiting membrane we can reasonably assume that the external surface of the bacterial cell is potentially lipoidal. In this connection it is interesting to recall the observation of Metchnikoff. Metchnikoff noted that the intestinal tract of the larva of moths was free from bacteria, and reasoned that this absence of intestinal flora must have some connection with the nature of the enzymes secreted in the gastro-intestinal tract. He calls attention to the fact that these insects, utilizing waxes and fats to a large extent, must secrete powerful lipases. If this supposition is correct, then bacteriolysis need not be related to proteolysis.

In order to obtain some information concerning the nature of bacteriolysis, we first made some investigations to determine the action of ferments such as trypsin and leucoproteose on bacteria. Kantorwicz, who has studied this subject most carefully confirms the older observations of the absence of digestion of the intact cells, whether living or dead, and showed that heating Gram-negative organisms to 70° C. made them lose their power of resistance, while Gram-positive organisms resist digestion even after boiling. He concluded that the resistance was due to an antiferment. He subsequently found that dried organisms were also resistant to digestion, but lose their resistance after being extracted with acetone.

Knowing that the unsaturated fatty acids are antitryptic, and that their inhibition is proportional to the degree of unsaturation, it seems reasonable to assume that bacteria might resist digestion in a degree proportional to the amount of unsaturation of the lipoids they contained. It will be remembered that Kantorowicz found that the antiferment was removed from the bacteria when they were ground up and extracted with acetone.

In experiments made with tubercle bacilli, we found that

their digestion by trypsin was in proportion to the amount of lipoids contained. Those organisms containing 31% of lipoids gave only 23% of digestion, while partially extracted bacilli which contained 7% gave 57% of digestion. These bacilli were old and had been killed by heating at high temperatures, and as a consequence some of the unsaturated fatty acids may have become oxidized. It is probable that recently grown organisms under these conditions would give still less digestion with trypsin. Similar results were obtained with other organisms, both Gram-negative and Gram-positive, and it was found in every instance that previous extraction with ether almost doubled the amount of digestion.

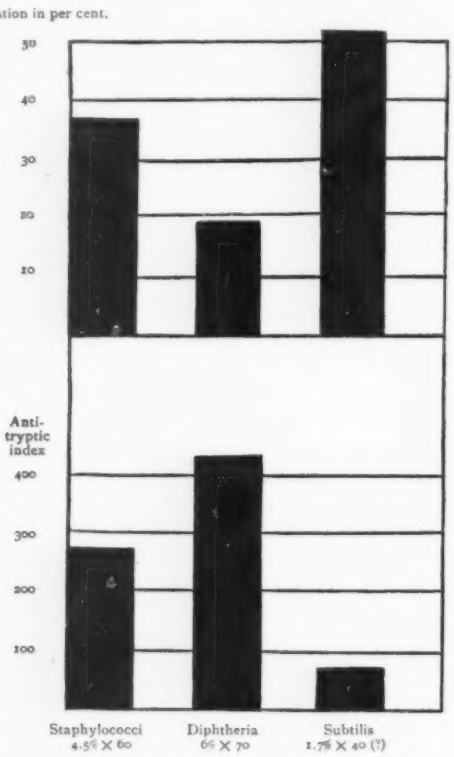

CHART 4.—**Relation of the antiferment index to the rate of digestion of Gram-positive organisms.**

The lipoids obtained by extracting various organisms with ether were saponified and tested for their antiferment properties, and in each case the ferment-inhibiting action of the soaps was found to be proportional to the degree of unsaturation.

We next studied the comparative rate of digestion of bacteria, in its relation to the contained lipoids. As a result of these experiments we found that we could determine the lipoidal antitryptic index by multiplying the percentage of lipoids by the iodin value. That is, those organisms containing a high percentage of lipoids with a high iodin value were always more resistant to the actions of ferments, and digestion was in inverse proportion to the figures obtained by multiplying these two factors. Thus, unextracted tubercle bacilli gave the highest figure according to this method and showed the smallest amount of digestion. The diphtheria bacilli came next, while subtilis bacilli showed the lowest figure and the largest amount of digestion. These statements hold true for all the organisms tested.

That the bacterial lipoids influence the intracellular proteolytic activity of bacteria becomes apparent when we compare the amount of non-coagulable nitrogen contained in various organisms. Thus diphtheria bacilli, with a high antiferment index, have only 5% to 7% of the nitrogenous material in a non-coagulable form, whereas in subtilis bacilli, with a low antiferment index, a correspondingly greater protease activity is indicated by the presence of 33% to 35% of the total nitrogen in a non-coagulable form. Staphylococci, typhoid bacilli, and colon bacilli occupy an intermediate position. This influence is analogous to the effect of the antiferment on the protein metabolism of higher organisms, as we shall show later.

The antiferment is probably the agent concerned in preventing excessive protease action, or autolysis, in the cells. It is easy to understand that in dead bacteria the antiferment property may be greatly lessened by changes in the state of dispersion of the lipoids brought about by the increase in acidity. This lowering of the antiferment property of the unsaturated lipoids by a change in their dispersion is most easily demonstrated with serum antitrypsin. The morphological expression of the process is possibly to be found in the development of the so-called myelin figures present in cells during the early stages of autolysis. Possibly the increase in the rate of autolysis following the addition of certain inorganic colloids to the liver emulsions, noted by Ascoli and Izar,[29] depends on adsorption of the lipoid antiferments.

It is probable that in Gram-positive organisms the lipoids are in more intimate association with the protein molecule, so that when dispersion changes are brought about, as by heating, the relative protection by these lipoids remains unaltered. This idea finds support in the fact that the lipoids from Gram-positive organisms resist extraction by lipoid solvents to a greater extent than those from Gram-negative bacteria.

BACTERIOLYSIS.

The relation of proteolytic ferments of the serum to immunity reactions, particularly to bacteriolysis, has interested numerous investigators, and in view of the recent work of Abderhalden and his collaborators, it merits attention quite apart from a theoretical consideration.

The study of possible proteolytic cleavage during bacteriolysis, because of the manifest technical difficulties entailed by the accurate determination of nitrogen in the small amounts available, has been limited to rather general statements, based in most instances on experiments carried out with the Sorensen method. This method, being an index of the total cleavage of the protein molecule, gives no information as to the change from coagulable to non-coagulable forms, and is used in estimating peptolytic or ereptic enzyme activity rather than pro-

teolytic changes. For a like reason it represents the splitting of the protein bodies to non-toxic fragments in contradistinction to the splitting of the whole non-toxic protein molecule to the higher non-coagulable but toxic forms (proteoses).

The bactericidal and bacteriolytic property due to the action of complement and ambocepter has been assumed, more particularly by French and German writers, to be enzymotic in character, and in the nature of a protease action. There is, however, no experimental basis for this idea; indeed the fact that complement action is not identical with protease action can be demonstrated in a very simple experiment. When chloroform is added to fresh serum and thoroughly mixed, the complement is rapidly destroyed; the serum protease, however, first becomes active under these conditions, as was first shown by Delezenne and Pozerski.[20] The activation of the ferment under the influence of chloroform or other lipoid solvents is due to the fact that the antiferment is removed. There should, therefore, be no confusion as to the non-identity of these serum constituents.

If complement activity is enzymotic in character, we should rather seek to identify it with the lipase or allied enzymes. The substrate offered for complement action—red blood cells, animal cells, bacteria—is lipoidal in nature, the potentially lipoidal character of the limiting membranes of the corpuscles and animal cells being well established and rendered more than probable for bacterial cells. The fact that powerful proteolytic enzymes are without effect on such substrata is almost conclusive evidence that the surface of these substrata are not protein in nature. The observations of Metchnikoff, to which we have already referred, are of special significance when we discuss the phenomenon of bacteriolysis.

The experiments,[21] designed to determine the amount of proteolysis occurring during bacteriolysis, were carried out with emulsions of washed bacteria. The bacteria after treatment with serum were centrifuged and washed, and the total nitrogen and non-coagulable nitrogen was determined in the sediment and in the supernatant fluid.

Briefly, the results of the experiments show that the greatest loss of bacterial nitrogen was in the mixtures containing immune serum and complement, indicating a marked lysis of the bacteria. There is, however, no corresponding increase in non-coagulable nitrogen obtained in the supernatant fluid. In other words, there is no relation between the amount of lysis and proteolysis.

In view of the established fact that the serum of practically all animals contains an active antiferment against trypsin, leucoproteose, and the autolytic ferments, we can hardly expect a result other than that noted in the above experiments; *i. e.*, that bacteriolysis is not associated with proteolysis.

One of us with Strouse has called attention to the fact that mere solution of bacteria should not be confused with proteolysis; the former might be due to purely physical factors, as when organisms are kept under lipoidal solvents as preservatives. This distinction should be made with equal emphasis for the immunity reactions.

If bacteriolysis is not associated with proteolysis we must find some other explanation. This, we believe, should be sought in the relation of the lipoids of the bacteria and the lipolytic effect of the serum. That a physical change of some sort is induced in corpuscles treated with immune serum and complement has been shown by Eisner and Friedemann,[22] and is indicated by the fact that bacterial organisms are rendered more digestible for trypsin.

Abderhalden Reaction.

Our results might be considered to contradict those obtained by several workers with the Abderhalden dialysis method, who have observed an increase in protein split products when bacteria were allowed to digest with immune serum (Voelkel).[23] These workers have ignored the presence of an excess of antiferment in the blood, assuming that proteolysis might take place under normal conditions with the resultant splitting of bacteria.

Numerous experiments made during the past year have convinced us that the same explanation applies to the Abderhalden reaction. Normal human serum rarely contains strong proteolytic ferments, and therefore does not give a positive Abderhalden reaction. On the other hand, sera of pregnant women, of patients with pneumonia, or with cachexia due to certain causes, do contain ferments and will give positive Abderhalden reactions.[24] We were able to obtain positive Abderhalden reactions with all human sera containing strong proteolytic ferments, regardless of the disease from which the patient was suffering, not only with placental tissue, but also by extracting the antitrypsin with chloroform, or adsorbing it with starch. In addition we found that those agents which adsorb antitrypsin most readily, are the ones which give the strongest Abderhalden reactions.

We must conclude from our results that proteolytic ferments capable of attacking only specific proteins, such as bacterial or placental proteins, do not exist. Proteolytic ferments are present in the blood under certain conditions, but they are not specific, and become evident only when the antitrypsin has been removed. A positive reaction is due to the adsorption of the antitrypsin by the placental tissue, or by the bacteria, and this permits the ferment to act on the exposed serum protein.

Protein Metabolism.

During the progress of this work we were impressed more than once with the possibility of a relation existing between the antiferment of the blood and the protein metabolism. Rosenthal[25] has demonstrated a decrease in the antiferment power of the blood of animals during starvation; the converse, an increase in the antiferment after feeding, had been noted by Zunz[26] and others. In view of the fact that Schulz,[27] and Heilner and Poensgen[28] have recently shown that during starvation a proteolytic ferment can be demonstrated in the blood in the period just preceding and during the high premortal excretion of nitrogen, we considered it of interest to ascertain in greater detail the alterations in the relative balance between ferment and antiferment in the serum of animals

during inanition." Both Schulz, and Heilner and Poensgen assume that the enzyme activity, which they have demonstrated, is due to the presence of a new ferment in the blood. The observation may, however, be interpreted as being simply due to a reduction of the antiferment with a resulting freeing of protease action.

Free protease action in the blood is not compatible with continued life because of the intoxication of the organism by the higher cleavage products of the proteins formed during hydrolysis. If during starvation such a state actually obtains, might it not be possible to explain the premortal rise in nitrogen excretion and the death of the animal itself on the basis of an autointoxication with protein split products?

Probably the most striking feature of the metabolic process during starvation is the so-called premortal rise in nitrogen excretion. Were this phenomenon due to a gradual attack on body proteins we might expect a correspondingly slow rise in nitrogen excretion. This, however, seldom occurs; the increase is sudden, almost explosive in character, and the excretion remains high until death occurs. Schulz has possi-

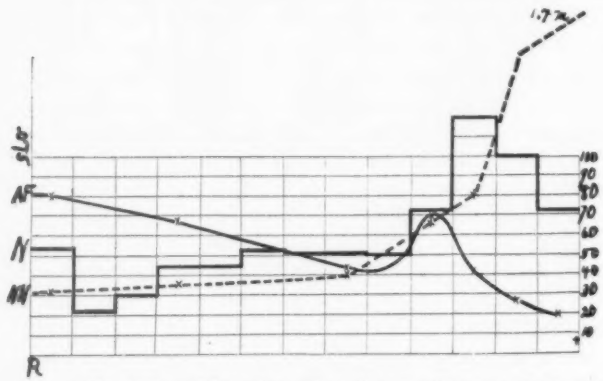

CHART 5.—*AF*, antitrypsin; *N*, urinary nitrogen; *NN*, non-coagulable nitrogen in 1 cc. of blood.

bly interpreted the picture most clearly. He assumes that during starvation we are dealing with either a low grade chronic intoxication, or a series of more acute shocks arising from toxic substances produced in the organism; the manifestations being occasional periods of fever, malaise and weakness. Schulz concludes that the final rise in nitrogen excretion is due to such an intoxication with resulting tissue destruction.

Our experiments were conducted with dogs and rabbits. The animals were kept in metabolism cages with constant access to water but without food. Care was taken to avoid unnecessary handling and to keep the temperature of the room constant. The small amount of blood needed was taken from the ear vein. Chart 5 shows graphically the results obtained with a rabbit.

In the first experiment the results of the alteration of the antiferment balance are readily seen. The gradual rise in the non-coagulable nitrogen is coincident with the gradual reduction of the antiferment, a reduction which continued until the 20th of July, when evidently the enzymotic power overbalanced the inhibitory, and the non-coagulable nitrogen began to rise rapidly. It is at this time that the intoxication begins, and during this period, too, it will be recalled, Schulz, and Heilner and Poensgen have shown the proteolytic activity of the serum. This protein intoxication is followed by a rise in antitrypsin, as is the case following anaphylaxis, anaphylatoxin, and serotoxin injections, or after burns; the injury to the cells resulting possibly in a liberation of unsaturated lipoids from the cells which then enter the circulation in a state of colloidal solution. These lipoids are, however, metabolized rapidly, the antitryptic titre falls while the non-coagulable nitrogen, representing the ferment action of the proteases, continues to rise at a rapid rate. The premortal rise in nitrogen excretion probably represents then a protein intoxication, an intoxication due to the lowering of the balance between the ferment and the antiferment, the consequent activation of ferments normally present, and the resulting formation of toxic split products from proteins. The short rise in antitrypsin following this intoxication is probably another manifestation of the same process. These experiments were repeated several times with dogs and rabbits and similar results obtained in each instance.

Apart from any clinical bearing, these experiments offer several confirmatory lines of evidence in regard to the nature of serum antitrypsin and its relation to the protein metabolism of the organism.

That the rate of protein metabolism is intimately influenced by the amount of antiferment in the blood is indicated by the following table, in which the average antitryptic index for the first five days of starvation of four rabbits is compared with the total amount of urinary nitrogen excreted:

Animal No.	Per Cent Inhibition	Nitrogen Excreted
1	41	4.24 gm.
2	66	2.95 "
3	71	1.97 "
4	73	1.99 "

The excretion of nitrogen seems to be inversely proportional to the antiferment index.

We can therefore understand that such substances as the iodides, which lower the antiferment, should be associated with an increase in protein metabolism, while egg fats and unsaturated oils—olive oil, cod-liver oil—will tend to increase the antiferment index and in this way depress protein metabolism, and so indirectly lead to a storage of nitrogen apart from any intrinsic food value in themselves.

The results of the experiments which we have just described tend to shed considerable light on the action of the iodides in causing absorption of necrotic material. Iodin has been used for years, yet little is known concerning its action in the body. This lack of knowledge applies particularly to its activity in causing the absorption of necrotic material such as is found in gummata.

The results obtained with iodides have been variously ascribed to their influence on the general metabolism of the body; to their supposed action in causing a lowering in blood pressure; to changes in the viscosity of the blood; to lympho-

cytosis; to an increase in the activity of the lymphatics and, to the oxidizing properties of nascent iodin.

Time will not permit us to discuss the work done by Binz,[40] Hinz,[41] Romberg,[42] Müller and Quada,[43] Determan,[44] Stockman and Charteris,[45] Lehndorff,[46] Macht,[47] and others, in regard to the pharmacologic action of iodin. McLean[48] made a study of the distribution of iodin in the bodies of rabbits which had received several doses of potassium iodide, and found that the lipoid fraction contained 32% and the water soluble fraction 67%, while the extracted protein contained no iodin. This work would seem to disprove the older view that iodin combines with the proteins of the body.

We confined our investigations to the action of iodin on the antitrypsin of the blood, as we believed that antitrypsin is the most important agent in preventing the absorption of necrotic material such as is found in infarcts and in caseous areas in syphilis and tuberculosis. The knowledge that the antiferments of the blood and of tuberculous caseous matter are

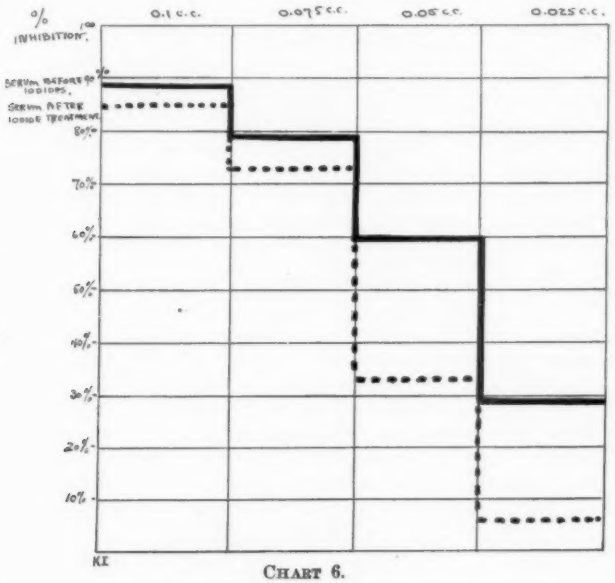

Chart 6.

unsaturated fatty acids, suggested to us the possibility that the action of iodin in the body may be due to its combination with these fatty acids, thus causing a neutralization of their activity as ferment-inhibiting agents. If this supposition is true, the neutralization of the activity of these agents should lower the anti-enzyme strength of tissues in general and permit the removal of dead tissue by autolysis.

We are indebted to Drs. Fordyce, McMurtey and Sharpe, of the Vanderbilt Clinic, New York City, for furnishing us with the clinical material used in this study. Thirteen patients were studied, 11 of whom were syphilitics. In each instance the blood was tested before iodides were given, and then at frequent intervals until the patient reached the limit of tolerance.

This series of cases is not large, but is sufficiently so to show that iodides administered to human beings cause a very considerable reduction in the antitryptic activity of the blood. The difference is not so evident when larger amounts of serum are used, as here there is an excess of the enzyme-inhibiting agent over that necessary to neutralize the amount of trypsin used; but in greater dilutions the difference is very obvious.

It is interesting to note that in the two patients of the series who developed iodism, the antiferment was very much higher than it had been during the course of treatment. This increase in antitrypsin may be due either to the failure of the iodin to combine with the unsaturated fatty acids, or to the mobilization of lipoids as the result of the toxic action of the iodin. Large doses of iodides may cause the neutralization of the antiferments in localized areas, or in the cell wall with the consequent destruction of cells by the ferments present and the liberation of lipoids. This may partially explain the toxic action of iodin.

Syphilis.

In order to arrive at some understanding concerning the action of iodin in syphilis two points must be considered: (1) Does it destroy the infecting organism? (2) Does it merely bring about resolution of the process and leave the infecting organism to produce similar lesions?

Authorities on this subject are unanimous in the belief that iodides are not curative in the sense that they prevent the return of the lesions, this can be accomplished only when the iodides are combined with some other form of treatment. Tomasczawaki[49] found that the administration of iodin does not prevent the development of experimental syphilis in monkeys and rabbits, neither has it a curative action; but iodized animals recovered quickly when given mercury.

As experimental work and clinical observations have demonstrated that iodides do not destroy the infecting organism, we must assume that the results obtained are due to the power the iodides possess of causing resolution of the lesions. That this actually occurs will be attested to by every clinician of experience.

Owing to its scarcity we have not been able to examine material from gummata, and so we are unable to state positively that the antienzymes present are similar to those found in tuberculous caseous material, but it is probable that the same agents are active here also as in anemic infarcts in which autolysis does not occur. If this assumption is correct, it is not difficult to explain why large gummata rapidly disappear when the patient is brought under the influence of iodides. It is due to the fact that unsaturated fatty acid radicals which inhibit autolysis, have become saturated with iodin. As soon as this occurs, the ferments which are present, or which may be brought in, become active, autolysis takes place, and the necrotic tissue is absorbed. Here, also, the local action of the ferments is made less difficult by the reduction of the antienzyme in the circulating blood. It must be borne in mind that the iodides are not as effective in the earlier stages of syphilis when necrosis of tissue is not so evident.

If the above interpretation of the action of iodin is correct it gives the clinician a rational idea of what he is accomplishing

when he gives iodides to a patient in the tertiary stage of syphilis. According to this view, iodin neutralizes the action of the agents which prevent resolution and absorption of the diseased or necrotic tissue, and at the same time lays bare to the action of the real germicidal agent the infecting organism which previously had been protected by necrotic tissue. With the exposure of the infecting organism, such agents as mercury and salvarsan would be much more effective.

BIBLIOGRAPHY.

1. Vaughan, V.: Boston Med. & Surg. Jour., 1906, CLV, 215, 243, 271.
2. Abderhalden, E.: Schutz-Fermente d. tierschen Organismus, 1912, S. 46.
3. Jobling, J. W. and Strouse, S.: Jour. Exp. Med., 1912, XVI, 269.
4. Opie, E. L.: Jour. Exp. Med., 1905, VII, 316, 759.
5. Müller, F.: Verhandl. d. XX Cong. f. Inn. Med., 1902, XX, 192.
6. Jobling, J. W. and Petersen, W.: Jour. Exp. Med., 1914, XIX, 239, 251, 383.
7. Jobling, J. W. and Petersen, W.: Jour. Exp. Med., 1914, XIX, 459.
8. Schwartz, O.: Wien. Klin. Wchnschr., 1909, XXII, 1151.
9. Sugimoto, T., Arch. f. Exper. Path. u. Pharmakol., 1913, LXXIV, 14.
10. Meyer, K.: Folia Serolog., 1911, VII, 472.
11. Kirchheim, L.: Arch. f. Exper. Path. u. Pharmakol., 1913, LXXIII, 374.
12. Jobling, J. W. and Petersen, W.: Jour. Exp. Med., 1914, XIX, 480.
13. Friedberger, E.: Ztschr. f. Immunitätsforsch., Orig., 1911, IX, 369.
14. Doerr, R.: Wien. Klin. Wchnschr., 1912, XXV, 331.
15. Friedemann, U.: Ztsch. f. Immunitätsforsch., Orig., 1909, II, 591.
16. Ströbel, H.: Compt. rend. Soc. de biol., 1911, LXXI, 413.
17. Bordet, J.: Compt. rend. Soc. de biol., 1913, LXXIV, 225.
18. Jobling, J. W. and Petersen, W.: Jour. Exp. Med., 1914, XX, 37.
19. Dold, H. and Aoki, K.: Ztsch. f. Immunitätsforsch., Orig., 1913, XVIII, 591.
20. Rusznjak, S.: Deutsche Med. Wchnschr., 1912, XXXVIII, 168.
21. Pfeifer, H. and Jarisch, A.: Ztsch. f. Immunitätsforsch., Orig., 1912-13, XVI, 38.
22. Jobling, J. W. and Petersen, W.: Jour. Exp. Med., 1914, XX, 468.
23. Jobling, J. W. and Petersen, W.: Jour. Exp. Med., 1914, XX, 452.
24. Kruse: Münch. Med. Wchnschr., 1910, LVII, 685.
25. Fermi, C.: Cent. f. Bakt., 1te Abt., Orig., 1909, LII, 252.
26. Kantorowicz, A.: München. Med. Wchnschr., 1909, LVI, 897.
27. Weinkopf, P.: Ztschr. f. Immunitätsforsch., Orig., 1911, XI, 1.
28. Czapek, F.: Biochemie der Pflanzen, 3te Aufl., Jena, 1913, 679.
29. Ascoli, M. and Izaar, G.: Biochem. Ztschr., 1907, V, 394; VI, 192.
30. Delezenne, C. and Pozerski, E.: Compt. rend. Soc. de biol., 1903, LV, 327.
31. Jobling, J. W. and Petersen, W.: Jour. Exp. Med., 1914, XX, 321.
32. Eisner, G. and Friedemann, U.: Ztschr. f. Immunitätsforsch., Orig., 1914, XXI, 520.
33. Voelkel, E.: München. Med. Wchnschr., 1914, LXI, 349.
34. Jobling, J. W. and Petersen, W. and Eggstein, A.: Jour. Exp. Med., 1915, XXI, 239.
35. Rosenthal, E.: Folia Serolog., 1910, VI, 285.
36. Zunz, E.: Bull. de l'Acad. de méd. de Belgique, 1905, XIX, 729.
37. Schultz, F. N.: München. Med. Wchnschr., 1913, LX, 2512.
38. Heilner, E. and Poensgen, F.: München. Med. Wchnschr., 1914, LXI, 402.
39. Jobling, J. W. and Petersen, W.: Ztschr. f. Immunitätsforsch., 1915.
40. Binz, E.: Arch. f. Exp. Path. u. Pharmakol., 1894, XXXIV, 185.
41. Hinz: Virch. Arch. f. Path. Anat., 1899, CLV, 44.
42. Romberg, E.: Verhandl. d. Cong. f. Inn. Med., 1904, XXI, 60.
43. Müller and Quada: Deutsche Med. Wchnschr., 1904, XXX, 1751.
44. Determann: Deutsche Med. Wchnschr., 1908, XXXIV, 871.
45. Stockman and Charteris: Brit. Med. Jour., 1901, II, 1520.
46. Lehndorff, R.: Arch. f. Exper. Path. u. Pharmakol., 1914, LXXVI, 224.
47. Macht: Bull. Johns Hopkins Hosp., 1914, XXV, 283.
48. McLean, F. C.: Arch. Int. Med., 1912, X, 505.
49. Tomasczawski: Deutsche Med. Wchnschr., 1910, XXXVI, 653.

DISCUSSION.

Dr. Howell: I do not feel well qualified to discuss Dr. Jobling's paper in a critical way, but I should like to express the great interest I have felt in it and to ask some questions. The fundamental facts presented by Dr. Jobling are in themselves interesting and suggestive, and of course the very wide application to nutritive conditions adds greatly to our feeling that we are dealing here with phenomena that may be very significant. As a student of the blood, my attention was attracted particularly by Dr. Jobling's statement that his sera freed from lipoid by chloroform show a strong tendency to produce intravascular clotting. As thin sera are cytotoxic, it is possible that they may have an immediate destructive effect on the blood-platelets and thus bring about intravascular coagulation. I should like to ask whether platelet counts were made after the injection of the washed serum. The protection conferred upon the living cell by the presence of lipoids with a high iodine value, as emphasized by Dr. Jobling, suggests naturally to the physiologist that herein may lie the explanation of the protection of the intestine from self-digestion by trypsin. The experiments seem to put this antiferment theory on a more probable and comprehensible basis. In regard to the application made of the facts to the explanation of the Abderhalden reactions, it is of course difficult to judge. Most physiologists have accepted the fundamental assumption underlying these reactions, namely, that the tissues can form protective enzymes. I should like to remind Dr. Jobling that this assumption seems to hold in the case of foreign carbohydrates injected into the blood as well as in the case of foreign proteins. Can the change in the antitryptic lipoid be used to explain both cases? The application made of his facts by Dr. Jobling to explain the ante-lethal rise in nitrogen excretion in the cases of prolonged starvation is quite novel to me. Physiologists had accounted for this phenomenon in an apparently satisfactory way by the assumption that it marked the period when the body-fat had been consumed and the animal was thrown upon his protein tissues alone. Both facts might of course be correct—the fall in antitrypsin might coincide or be connected with the consumption of body-fat, or it may be that they are entirely independent. I should like to ask Dr. Jobling whether experiments have been made that rule out the older explanation. Dr. Jobling's ideas are certainly stimulating. The possibilities that suggest themselves on the basis of this balance between the proteolytic and protective enzymes to the body are many and I have no doubt that they will call out a great deal of investigation.

DR. JOBLING: I am glad that Dr. Howell brought up the subject of specific ferments for foreign carbohydrates. In using the terms ferment and antiferment I was referring only to proteases and antiproteases. We have not done any work with the carbohydrates. We cannot accept Abderhalden's statements of having demonstrated the presence of specific immune ferments for carbohydrates. All the work done in immunity shows that immune substances are not present in the circulating blood for several days after an animal has been inoculated with the foreign substance. Abderhalden, however, found that the sera became active a few hours after the animals were inoculated. We believe that his work indicates that these ferments are normally present in the body, but are mobilized only when the foreign carbohydrates are introduced into the general circulation.

Dr. Howell's suggestion that the intravascular clotting may be due to the destruction of platelets by the extracted sera is very interesting and may prove to be the explanation. Platelet counts were not made. Von Behring has recently advanced the view that the intoxication in anaphylaxis is due to thrombi composed of coagulated platelets.

Our inanition experiments were conducted to determine the relation of the serum ferments and antiferments to the nitrogen excretion. We had already shown that sera containing proteases become toxic if the antiferments were removed and it seemed reasonable to assume that the same thing occurred in the body, as the maximum nitrogen output in the animals corresponded in time with the minimum amount of antiferment. We were under the impression that Lusk and others had shown that an animal may die of starvation while the body still shows considerable fat.

NOTE ON THE ANTAGONISM BETWEEN THE LACTIC-ACID AND THE SPORE-BEARING ORGANISMS IN MILK.

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It has now been shown by a number of observers that the predominant organism in milk is the lactic acid bacterium known usually as *Streptococcus lacticus* for which, however, the name *Bacterium guntherii*, Lehmann and Neumann, is probably the correct designation.[1] Under normal circumstances these organisms multiply and crowd out the aërobic and anaërobic spore-bearing bacteria. If the lactic acid organisms are destroyed by heating the milk to a temperature of 70° C., however, the spore-bearing organisms multiply rapidly.[2] It becomes a matter of interest, therefore, to study more carefully the series of changes occurring in the aërobic bacteria in milk heated to various temperatures below 70° C. To determine these changes samples of market milk were heated to temperatures ranging from 55° C. to 70° C. for 30 minutes and cultures made at various intervals. The results obtained from the examination of a considerable number of samples may be summarized as follows:

Plates poured from raw milk reveal usually a mixture of lactic acid bacteria, pigmented air organisms, and intestinal species which may be placed in the coli-aërogenes group. Only rarely did colonies of spore-bearing bacteria appear on the plates. If this milk be incubated at 37° C., it clots firmly and cultures show a multiplication of the lactic acid organisms and the coli-aërogenes forms to the general exclusion of the pigmented and spore-bearing species. By the end of from 48 to 72 hours the lactic acid organisms are usually predominant but the intestinal forms may also persist. Milk heated to 55° C. for half an hour shows on plates poured immediately a mixture of lactic acid organisms, intestinal forms and sporulators. The last form an appreciable feature and in this respect the plates differ essentially from the raw milk plates in which the sporulators are rare. When this milk is incubated it also clots in the manner of raw milk and plates poured at the end of 24 hours reveal no spore-bearing bacteria. These species have evidently been overgrown by the lactic acid organisms and the representatives of the coli-aërogenes group. Milk heated to 57.5° C. reveals practically the same phenomenon. At 60° C., however, a distinct change in the sequence of events is evident. On plates made immediately after heating, the spore-bearing bacteria are almost as abundant as the non-spore-formers. At the end of 24 hours the milk is usually firmly clotted and cultures show the two groups of organisms in about the same relative abundance. Soon peptonization sets in and eventually the clot in the milk completely disappears. Cultures after 48 to 72 hours reveal an increase of the lactic acid bacteria and the intestinal forms with a coincident disappearance of the sporulators. This change in the clot is probably to be ascribed to the peptonizing action of the spore-bearing aërobic and anaërobic bacteria, many of which secrete energetic peptonizing ferments. The disappearance of the sporulators may be due primarily to the rapid multiplication of the lactic acid organisms. It must also be remembered that *Bacterium welchii* (*B. aërogenes capsulatus*) is always present in milk and multiplies in milk heated to 60° C. It may also take part in the destruction of the sporulators, since, from the work of Shippen,[3] we know that such an action is possible. Whatever be the causation of the phenomenon, milk heated to 60° C. reveals a clotting usually followed by complete peptonization with a coincident multiplication of lactic acid organisms, so that by the end of 48 to 72 hours the aërobic plates show only these forms. This reaction is not universal, however, and at times the firm clot which is seen at the end of 24 hours, remains unaffected, probably as the result of the survival of sufficient numbers of lactic acid organisms to prevent the multiplication of both the aërobic and anaërobic spore-bearers.

In milk heated to 63° C. and to 65° C. the same phenomenon is seen. The milk first clots and then rapidly peptonizes, while cultures show the sporulators gradually yielding to the intestinal and lactic acid bacteria. At 67° C. the last two groups

are usually completely destroyed and in milk heated to this temperature the spore-bearers multiply rapidly. After peptonization has been completed, however, the aërobic cultures are frequently sterile and in such instances the destruction of the sporulators is best ascribed to the multiplication of *B. aërogenes capsulatus.*

From the various observations the following conclusion may be drawn.

CONCLUSION.

The heating of market milk to temperatures ranging from 55° C. to 65° C. for 30 minutes results in a destruction of many of the lactic acid and intestinal bacteria, and in such samples sporulating bacteria can always be found on the plates poured within 24 hours. After this time the lactic acid and the intestinal bacteria become the predominant species in the milk. The disappearance of the spore-bearers is to be attributed to the growth of the lactic acid organisms in some instances, to *Bacterium welchii* in others, and possibly is due to their combined action. At 67° C. the lactic acid and intestinal bacteria are usually completely destroyed and in milk heated to this temperature the spore-bearing organsims multiply rapidly from the start, but may at times yield to the "gas bacillus" in which case aërobic cultures may be sterile.

BIBLIOGRAPHY.

1. Shippen: Principal Types of Micro-Organisms in Baltimore Milk. Johns Hopkins Hosp. Bull., April, 1914, XXV, No. 278, 122.
2. Ford and Pryor: Observations Upon the Bacteria Found in Milk Heated to Various Temperatures. Johns Hopkins Hosp. Bull., Sept., 1914, XXV, No. 283, 270.
3. Shippen: Johns Hopkins Hosp. Bull., July, 1915.

BOOKS RECEIVED.

University of Pennsylvania. Contributions from the Department of Neurology and the Laboratory of Neuropathology for the Years 1913 and 1914. (Reprints.) Vol. VII. 4°. Philadelphia.

Surgery of the Blood Vessels. By J. Shelton Horsley, M. D., F. A. C. S. Illustrated. 1915. 8°. 304 pages. C. V. Mosby Company, St. Louis.

The Intervertebral Foramina in Man. The Morphology of the Intervertebral Foramina in Man, Including a Description of their Contents and Adjacent Parts with Special Reference to the Nervous Structures. (Supplement to "The Intervertebral Foramen.") By Harald Swanberg. With an introductory note by Prof. Harris E. Santee. Illustrated by 11 original full-page plates. 1915. 8°. 95 pages. Chicago Scientific Publishing Co., Chicago, Illinois.

Occupational Affections of the Skin. A Brief Account of the Trade Processes and Agents Which Give Rise to Them. By R. Prosser White, M. D. (Ed.), M. R. C. S. (Lond.). 1915. 8°. 165 pages. Paul B. Hoeber, New York.

Ninth Biennial Report of the Board of Control of State Institutions of Iowa. For the period ending June 30, 1914. 1914. 8°. 621 pages. Des Moines.

War Surgery. By Edmond Delorme. Translated by H. De Meric. With illustrations. 1915. 12°. 248 pages. Paul B. Hoeber, New York.

The Gynecology of Obstetrics. An Exposition of the Pathologies Bearing Directly on Parturition. By David Hadden, B. S., M. D. 1915. 8°. 198 pages. Macmillan Company, New York.

Reports from the Laboratory of the Royal College of Physicians, Edinburgh. Edited by J. J. Graham Brown, M. D., and James Ritchie, M. D. 1915. Vol. XIII. Oliver & Boyd, Edinburgh.

Modern Medicine. Its Theory and Practice. In Original Contributions by American and Foreign Authors. Edited by Sir William Osler, Bart., M. D., F. R. S., and Thomas McCrae, M. D. Vol. V. Diseases of the Nervous System; Diseases of the Locomotor System. Second edition, thoroughly revised. Illustrated. 1915. 8°. 1092 pages. Lea & Febiger, Philadelphia and New York.

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